Investigation into the Use of 1,2-Diamines in Fused Heterocycle Synthesis

A Thesis Presented by

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In Part Fulfilment of the Requirement for

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I, Adam Noble confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

The introductory chapter of this thesis gives a brief outline of the literature concerning the importance of 1,2-diamines. This includes their biological significance, their successful application to synthetic chemistry, especially in asymmetric synthesis, and methods available for their preparation. One particular method, the nitro-Mannich reaction, is reviewed in more detail. The synthetic utility of the products of the nitro-Mannich reaction is demonstrated by their application to the synthesis of natural products and pharmaceutical agents. Improvements to the scope of the nitro-Mannich reaction through the development of conjugate addition nitro-Mannich reactions are also discussed, including a brief outline of the methods available for asymmetric conjugate additions to nitroalkenes. The introductory chapter closes with the importance of 1,2-diamine-containing fused heterocycles, especially in pharmacological compounds, and describes some of the methods available for their preparation.

The results and discussion chapter gives a detailed account of the work that has been performed towards the development of an expedient synthesis of 1,2-diamine-containing fused heterocycles. The synthesis utilises a highly *anti*-selective reductive nitro-Mannich reaction to form structurally complex *β*-nitroamines in high yield. These are subsequently reduced to the corresponding 1,2-diamines, which undergo a palladium catalysed intramolecular *N*-arylation to synthesise an array of fused heterocyclic compounds. This cyclisation reaction can be performed highly selectively to form both 2-aminomethylene indolines and 3-aminotetrahydroquinolines through the use of a trifluoroacetyl protecting group. Details of the optimisation studies for the nitro-Mannich, nitro reduction and intramolecular *N*-arylation reactions are given. Investigations into the further derivatisation of the heterocyclic products are also presented. Finally, investigations into the development of an alternative synthesis of tetrahydroquinolines utilising an intramolecular nitro-Mannich reaction are discussed.

The conclusions drawn from the research have been summarised and future investigations to be carried out discussed, including the application of this new methodology to the synthesis of schizozygine. The experimental section presents detailed preparative methods and analytical data for all novel compounds. Finally, X-ray crystallographic data and a comprehensive list of references are provided in the appendices section.

Acknowledgements

Firstly, I would like to thank my supervisor Jim Anderson for giving me the chance to work on such an interesting project. I have thoroughly enjoyed my time in the Anderson group and that is due in part to his infectious enthusiasm for chemistry and his laid back attitude.

My appreciation also goes out to my fellow Anderson group members (both past and present) who have contributed greatly to me having such an enjoyable PhD experience. Regular coffee breaks, pub outings and general procrastination are indeed the best way to survive a PhD in organic chemistry.

I must also give my thanks to my industrial supervisors Ian and Seb who were very accommodating during my placement in Stevenage and have participated in some very interesting discussions during our meetings at GSK. Also, as I am no stranger to collecting the odd bit of data, I need to thank the support staff at UCL for keeping me well supplied with NMR, mass spec and elemental analysis data.

Thank you also to my family who have shown me nothing but support since I began at university. I thank my Mum for still spoiling me when I go home and my Dad for his words of wisdom. I also thank my sister and brother-in-law, Vanessa and Ricardo, for their constant support.

And finally, my thanks go to Laura, my best friend and wife. She has become as adept at humouring me during my chemistry monologues as I have during hers on dietetics. Apart from that, she always makes me smile, even if I don't want to, and I look forward to our future together.

See you all Stateside!

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Chapter 1: *Introduction*

1.1 Introduction

The development of novel methodologies in organic synthesis over the years has brought about an astounding array of useful chemical transformations. These have provided the synthetic chemist with the tools required to tackle even the most challenging of syntheses. Through the advent of new procedures for the synthesis of relatively simple motifs we can continue to improve the efficiency of syntheses of important compounds, such as natural products and pharmaceuticals, whose biological activities arise from the motifs that form the basis of their structures. One such motif is the 1,2-diamine which is found in a wide variety of important biologically active compounds. It is the synthesis of 1,2-diamine containing compounds that is the subject of the work presented in this thesis. The aim of this introductory chapter is to present a brief review of the literature concerning this topic. The first section focuses on the importance of 1,2-diamines and the methods available for their preparation. The second will discuss one particular method for their synthesis, the nitro-Mannich reaction, which has in recent years been developed into a powerful synthetic tool. The final part will focus on the importance of fused nitrogen heterocycles, especially those containing 1,2-diamines, the synthesis of which is the focus of the research presented herein.

1.2 1,2-Diamines

The 1,2-diamine structural motif is found in a wide variety of compounds displaying a broad spectrum of interesting biologically activities. These compounds range from natural products, including those which perform essential metabolic functions within the human body; to synthetic (unnatural) products, which have become important medicinal agents in the treatment of a variety of diseases. The importance of this simple functional group has further been demonstrated with its application to asymmetric synthesis, including both transition metal catalysed and organocatalytic transformations. Consequently, there have been numerous strategies developed for the synthesis of 1,2-diamines, including diastereo- and enantioselective examples, with continued efforts to improve their efficiency and selectivity being made today.

1.2.1 Biologically Active 1,2-Diamines

There are a huge number of biologically active natural products that contain 1,2-diamines, many of which have been employed as medicinal agents for the treatment of a variety of diseases.[1] One particularly notable example of a biologically active 1,2-diamine is biotin (vitamin H, **1**), which is a co-enzyme of carboxylases that carry out essential metabolic reactions within the human body.[2] It is one of a large number of natural products containing the *n*,*n*+1-diaminocarboxylic acid substructure **2**. For example, 2,3-diaminopropanoic acids are found in a range of important compounds such as the glycopeptidic bleomycins, which are used as chemotherapeutic agents for the treatment of malignant lymphomas and squarmous cell carcinomas,[3] and the well known penicillin-type antibiotics **3** (Figure 1).[1]

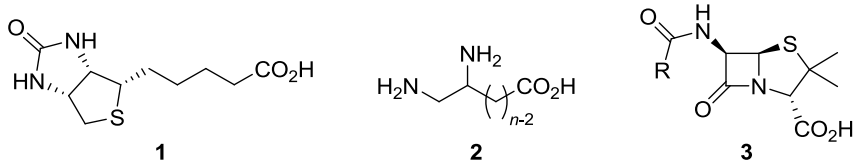


Figure 1: Natural products containing *n*,*n*+1-diaminocarboxylic acids.

The number of natural products containing 1,2-diamines is far from limited to those containing *n*,*n*+1-diaminocarboxylic acids. Bioxalomycin $\alpha 2$ (**4**) has demonstrated potent antimicrobial and antitumor activity,[4] ecteinascidin 743 (**5**) is prescribed for the treatment of soft tissue sarcoma and balanol (**6**) is a potent inhibitor of protein kinase C (Figure 2).[5,6]

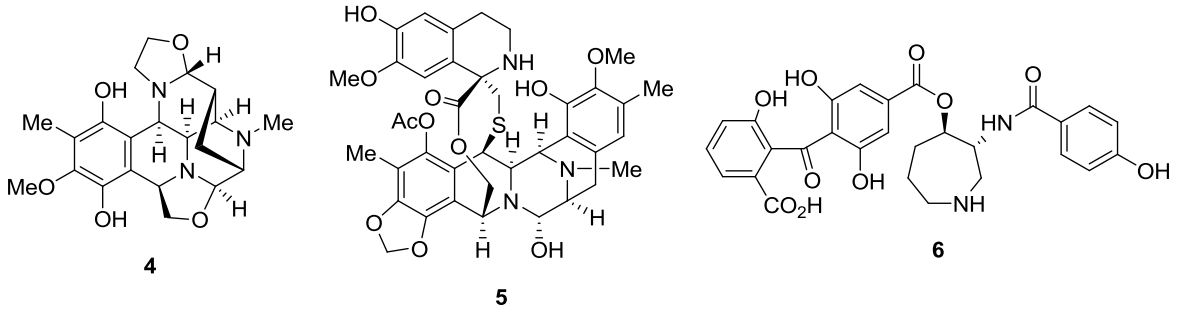


Figure 2: Natural products containing 1,2-diamines.

Given the wide range of biological activities demonstrated by these 1,2-diamine containing natural products, it is no surprise that a large number of unnatural 1,2-diamine containing medicinal agents have been reported.[7] Examples include the potent κ-opioid agonist ICI-199441 (**7**), which demonstrates the same analgesic response as morphine but without the addictive side effects;[8] (-)-oseltamivir phosphate (Tamiflu™, **8**), used for the treatment

of avian flu virus H5N1;[9] and the semi-synthetic penicillin flucloxacillin (Floxapen™, **9**), which has superior activity against penicillin-resistant *staphylococci* than other isoxazole penicillins in clinical use prior to its development (Figure 3).[10]

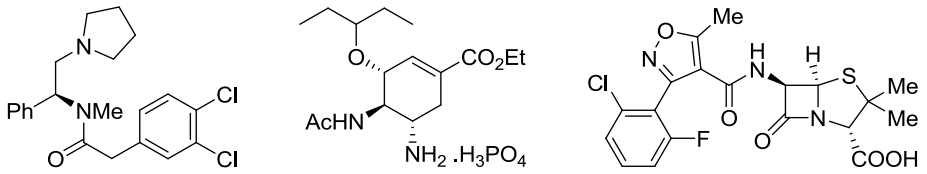


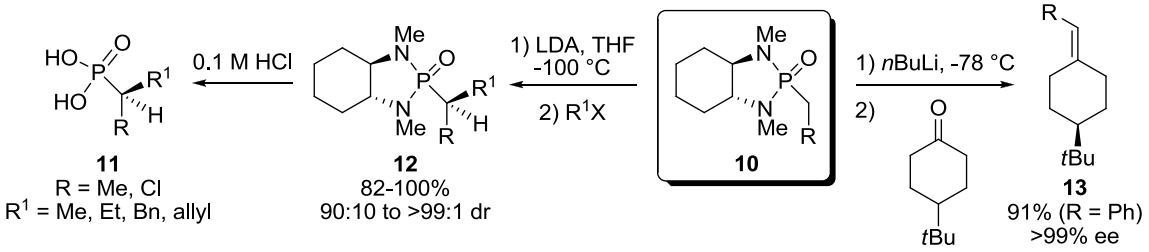
Figure 3: Unnatural products containing 1,2-diamines.

1.2.2 Synthetic Applications

The importance of 1,2-diamines in organic synthesis, especially in asymmetric reactions, has been demonstrated through their successful application as chiral auxiliaries, chiral ligands and organocatalysts. They have a wide range of uses ranging from simple diamines such as TMEDA, widely used as an additive to stabilise and activate organometallic reagents and inorganic salts, to complex organocatalysts capable of performing highly enantioselective transformations.[1]

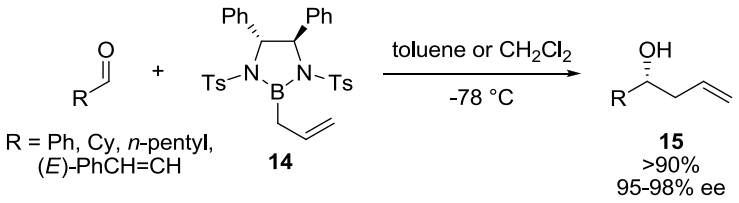
1.2.2a Chiral Auxiliaries

A number of chiral auxiliaries derived from 1,2-diamines have been employed in highly diastereoselective reactions. Hanessian's group has demonstrated the use of chiral bicyclic phosphonamides **10** as chiral auxiliaries in the synthesis of chiral α-alkyl phosphonic acids **11** by asymmetric alkylation and subsequent hydrolysis of phosphonamide **12** (Scheme 1).[11] The same group also reported the asymmetric olefination of cyclohexanones using phosphonamide **10** to form benzylidene cyclohexanes **13** in excellent ee (Scheme 1).[12]



Scheme 1: Chiral bicyclophosphonamides **10** as chiral auxiliaries.

Corey *et al.* developed allylborane **14**, derived from (*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine, for the asymmetric allylation of aldehydes. The synthesis of a variety of homoallylic alcohols **15**, in excellent yield and enantioselectivity, was reported (Scheme 2).[13]

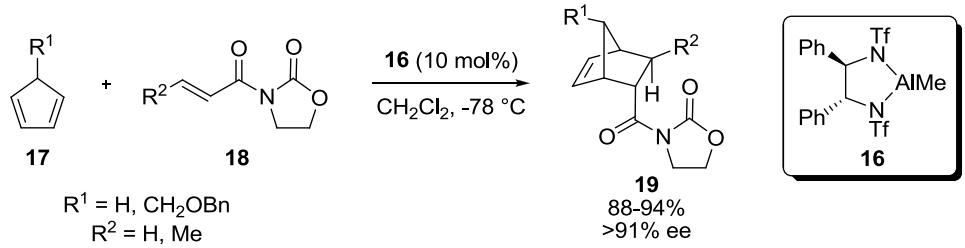


Scheme 2: Asymmetric allylation of aldehydes with chiral 1,2-diamine derived allylborane **14**.

1.2.2b Transition-metal catalysis

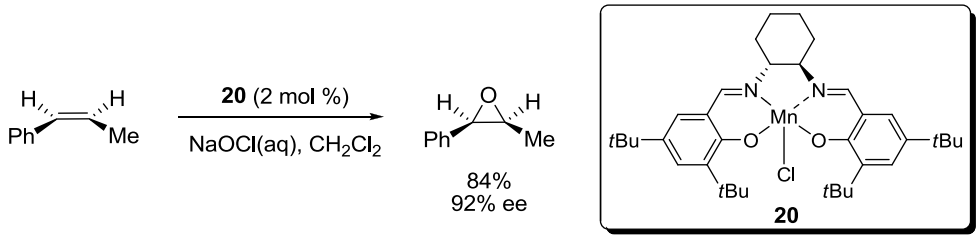
The application of 1,2-diamines to transition metal catalysis has also been extensively studied as a result of their ability to effectively chelate to metals. They have been used in a variety of reactions including alkylations, aldol reactions, conjugate additions, cycloadditions, asymmetric hydrogenations, epoxidations, dihydroxylations and aziridinations.[1] Some representative examples are given below.

Corey *et al*. demonstrated that the chiral diazaaluminolidine **16**, based on a similar design to allylborane **14**, acted as an efficient Lewis acid catalyst for asymmetric Diels-Alder reactions. The reaction of cyclopentadienes (**17**) with acrylamide derivatives (**18**) formed the desired cycloaddition products (**19**) in excellent yield and enantioselectivity (Scheme 3).[14]



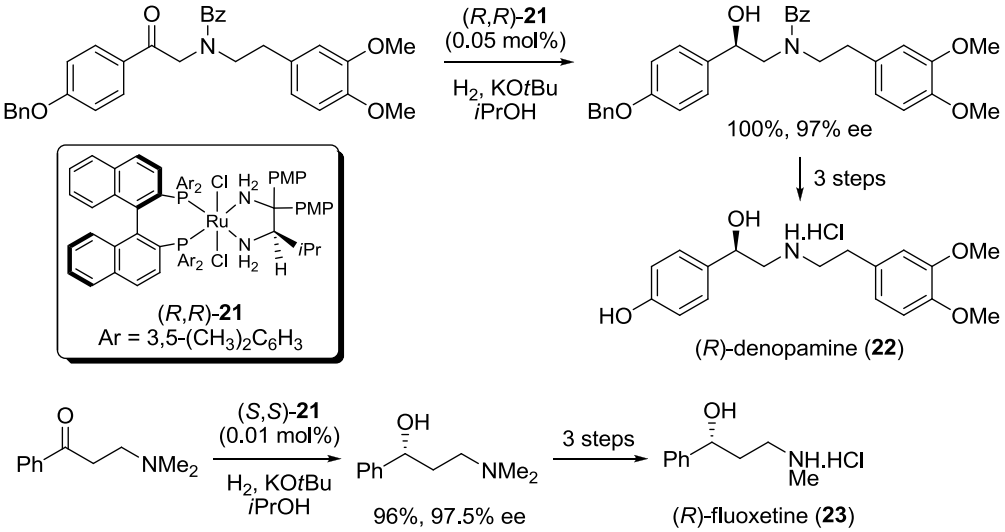
Scheme 3: Asymmetric Diels-Alder reaction catalysed by 1,2-diamine catalyst **16**.

The well-known Jacobsen epoxidation, an effective method for the asymmetric epoxidation of unfunctionalised alkenes, utilises manganese(III)-salen complex **20** derived from 1,2-diaminocyclohexane (Scheme 4).[15]



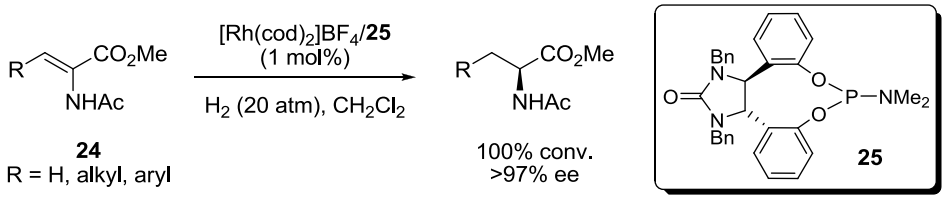
Scheme 4: Jacobsen epoxidation.

The recipient of the 2001 Nobel Prize in chemistry, Ryoji Noyori, extended the use of his Ru(II)-BINAP hydrogenation catalysts to the selective reduction of prochiral ketones by incorporating a chiral 1,2-diamine ligand.[16] The Ru(II)-BINAP/diamine catalyst (**21**) is extremely efficient and has been applied to the synthesis of a number of pharmaceuticals including (*R*)-denopamine **22**, a β_1-receptor agonist used to treat congestive heart failure, and (*R*)-fluoxetine **23**, an antidepressant (Scheme 5).[16c]



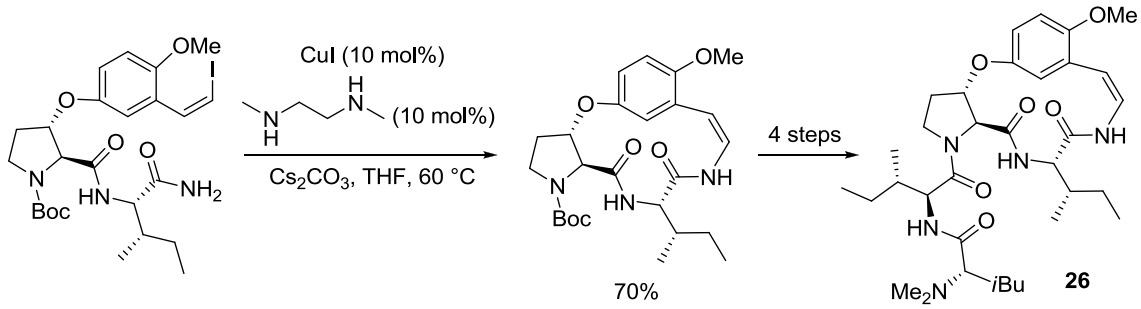
Scheme 5: Noyori hydrogenation.

Ding *et al.* reported the highly enantioselective Rh(I)-catalysed hydrogenation of dehydro-α-amino acid derivatives (**24**) and acetyl enamides using the chiral 1,2-diamine phosphoramidite ligand **25**. The hydrogenations proceeded with quantitative conversion and excellent enantioselectivity (Scheme 6).[17]



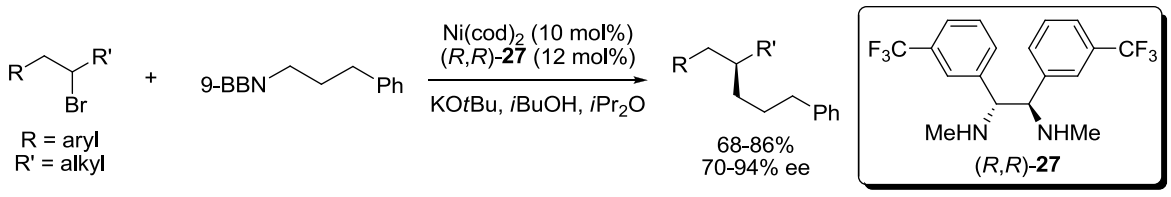
Scheme 6: Rh(I)-catalysed asymmetric hydrogenation with phosphoramidite **25**.

A more recent application of 1,2-diamines as ligands in transition metal catalysis is in cross-coupling reactions. Buchwald *et al.* demonstrated that the use of simple 1,2-diamine ligands, such as *N*,*N*'-dimethylethylenediamine and 1,2-diaminocyclohexane, in Cu(I)-mediated amidations of arylchlorides allowed these reactions to be performed under much milder conditions (weak base, non-polar solvent, lower temperature and catalytic copper) than those previously reported.[18] The robustness and functional group tolerance of these reactions have resulted in their application to the synthesis of several complex natural products, including paliurine F (**26**) by the group of Evano (Scheme 7).[18b]



Scheme 7: Cu(I)-diamine-catalysed amidation in Evano's synthesis of paliurine F (**26**).

Fu *et al.* developed a stereoconvergent Ni(II)/diamine-catalysed Suzuki cross coupling reaction of unfunctionalised racemic alkylbromides with alkylboranes that uses the 1,2-diphenylethylenediamine based ligand **27** (Scheme 8). The scope of this reaction has been expanded to include alkylhalides bearing nitrogen- and oxygen-containing functional groups.[19]

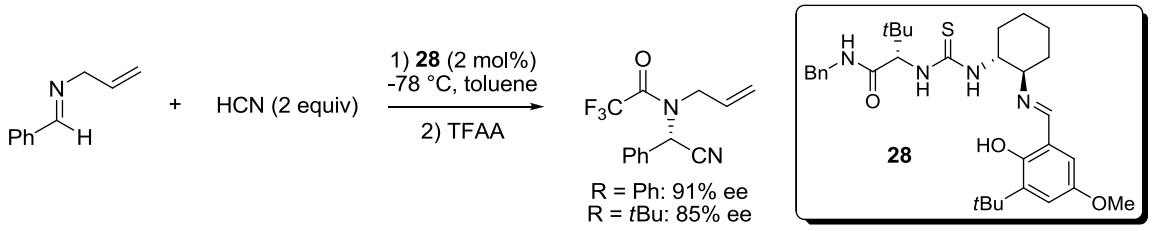


Scheme 8: Fu's Ni(II)-catalysed Suzuki cross-coupling reactions.

1.2.2c Organocatalysis

Since the re-introduction of the field of organocatalysis around the turn of the century there has been an explosion of interest from research groups around the world. The development of new organocatalysts has been a very attractive field in organic chemistry as they are stable in air and water, inexpensive and easy to prepare, simple to use and non-toxic.[20] Due

to the availability of simple chiral 1,2-diamines in both enantiomeric forms they have been applied to the generation of a wide variety of novel organocatalysts that catalyse a range of asymmetric transformations.[21] One family of organocatalysts that have benefited from the incorporation of a chiral 1,2-diamine are the bifunctional thiourea-based organocatalysts. These were first introduced by Jacobsen in 1998 who used 1,2-diamine-containing thiourea **28** to catalyse asymmetric Strecker reactions (Scheme 9).[22]



Scheme 9: Strecker reactions catalysed by chiral thiourea **28**.

Catalysts of this type have since been developed for use in a variety of asymmetric reactions. Several representative examples are given in Figure 4. Jacobsen's group went on to expand the scope of thiourea catalysed reactions to Pictet-Spengler and acyl-Mannich reactions through the development of catalyst **29**.[23] Simplified catalyst **30**, originally developed by Takemoto, has been used in a variety of conjugate addition and nitro-Mannich reactions.[24,25] Cinchona based catalyst **31** was developed independently by the groups of Soós, Connon and Dixon for use in various conjugate addition reactions.[26] The bisthiourea-guanidinium ion **32** was identified by Nagasawa as an effective catalyst for enantioselective Henry reactions of aliphatic aldehydes.[27]

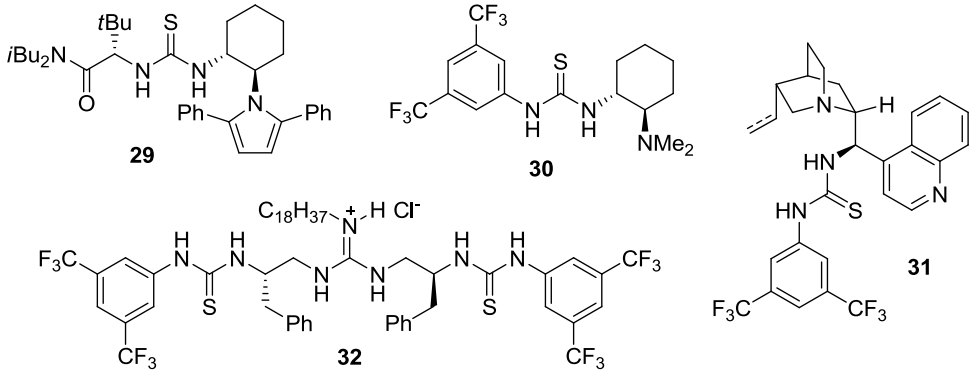
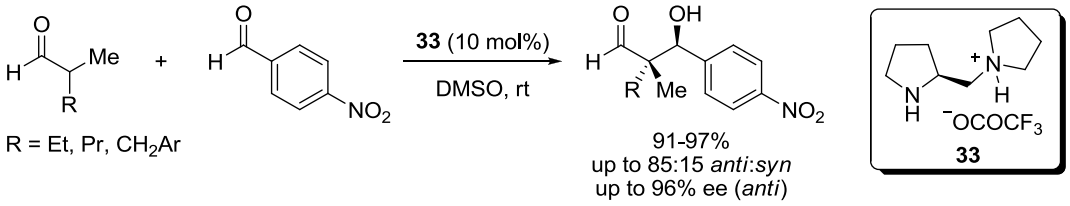


Figure 4: Examples of 1,2-diamine-containing thiourea catalysts.

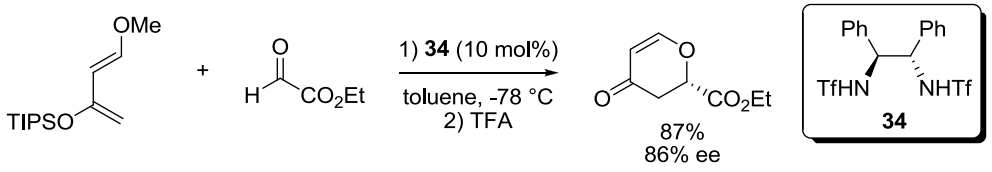
Organocatalysts not containing thioureas have also made use of 1,2-diamines. Proline-derived diamine catalyst **33** has been shown by Barbas *et al.* to have improved reactivity to proline in aldol reactions.[28] The reactions also exhibited improved reaction scope, allowing

for the enantioselective synthesis of quaternary stereocentres in reactions of *α,α*-disubstituted aldehydes with aromatic aldehydes (Scheme 10).

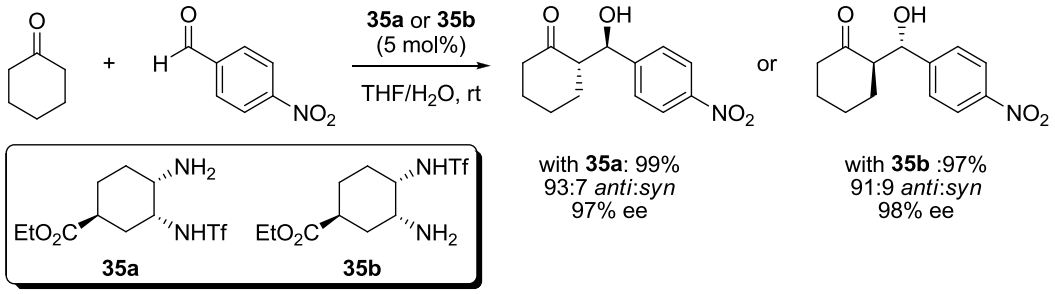


Scheme 10: Aldol reaction catalysed by proline-based diamine catalyst **33**.

The group of Mikami was able to show that even the simple diamine **34** was an active catalyst capable of inducing high enantioselectivity in hetero-Diels-Alder reactions between Danishefsky's diene and glyoxylates (Scheme 11).[29] Likewise, Maruoka *et al.* showed that the simple substituted 1,2-diaminecyclohexane catalysts **35a** and **35b** were excellent catalysts for the direct aldol reaction of cyclic ketones with benzaldehydes (Scheme 12).[30] The group were able to show that by switching between catalysts **35a** and **35b** they could reverse the selectivity of the aldol reaction, providing both enantiomers of the *anti*-aldol products.



Scheme 11: Hetero-Diels-Alder reaction catalysed by 1,2-diamine catalyst **34**.



Scheme 12: Aldol reaction catalysed by diamines **35a** and **35b**.

1.2.3 Synthesis

The prevalence of the 1,2-diamine motif in the structures of catalysts and biologically active compounds has led to the development of numerous methods for their synthesis. These can be categorised by the manner in which the two nitrogen atoms are introduced into the product 1,2-diamine. They include (1) the formation of a single C-N bond by introducing a single nitrogen atom onto a substrate already containing one nitrogen atom; (2) the simultaneous formation of two C-N bonds to introduce two nitrogen atoms onto a carbon skeleton; (3) the formation of a C-C bond between two nitrogen containing substrates (Figure 5).

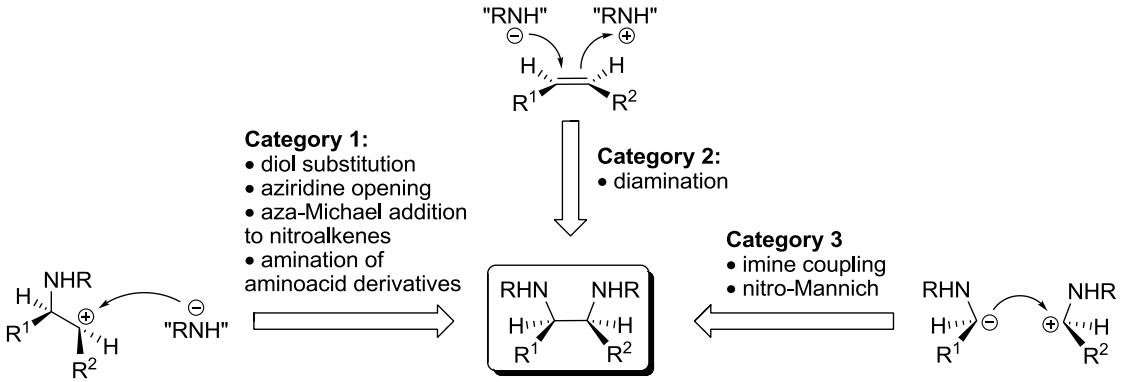
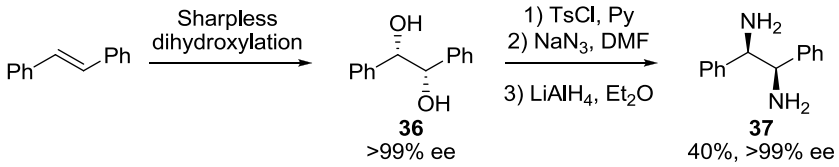


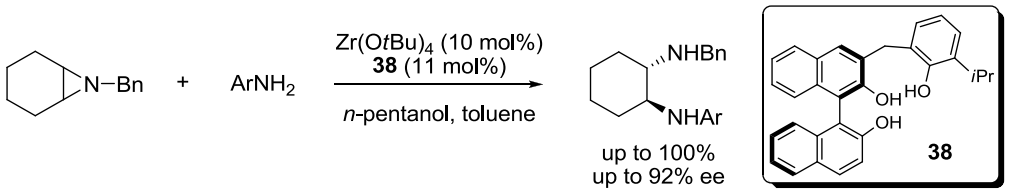
Figure 5: Categories of 1,2-diamine synthesis.

The first category involves a number of possible pathways to form the desired compounds, often with high levels of selectivity. These include substitution of 1,2-diols and opening of aziridines with nucleophilic nitrogen reagents, amination of α-aminoacid derivatives and aza-Michael additions to nitroalkenes. The efficiency and scope of osmium-catalysed asymmetric dihydroxylation reactions allows access to various enantiopure 1,2-diols that can be converted into enantiopure 1,2-diamines by double displacement with nitrogen nucleophiles. Salvadori and co-workers demonstrated this through an efficient synthesis of (*R*,*R*)-1,2-diphenyl-1,2-diamine (**37**).[31] Conversion of enantiopure diol **36** to the bis-tosylate followed by displacement with sodium azide and reduction of the resulting diazide gave enantiopure diamine **37** (Scheme 13).

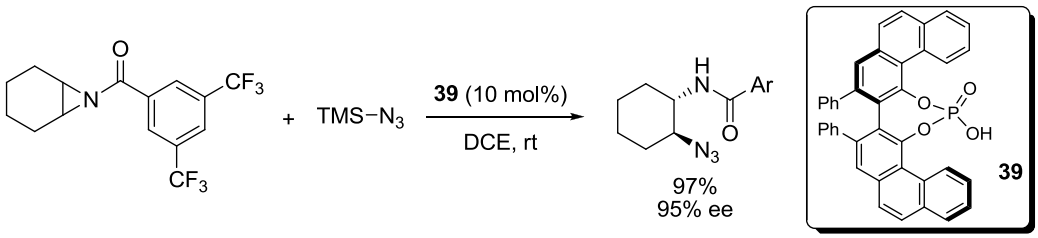


Scheme 13: Synthesis of 1,2-diamines from 1,2-diols.

The opening of aziridines with nitrogen nucleophiles has received considerable attention as it provides rapid access to 1,2-diamines.[32] Kobayashi *et al.* recently reported the enantioselective ring opening of *meso*-aziridines with a variety of anilines catalysed by a chiral zirconium catalyst derived from triol **38** (Scheme 14).[32b] There have also been numerous studies into the enantioselective ring opening of aziridines with azides. The group of Antilla investigated the use of TMS-azide in aziridine ring openings catalysed by chiral Brønsted acid **39** (Scheme 15).[32f] The aminoazide products could be reduced to give highly enantioenriched 1,2-diamines.



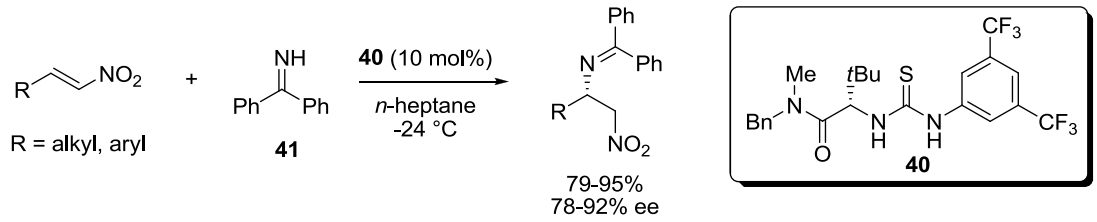
Scheme 14: Enantioselective ring opening of *meso*-aziridines with anilines.



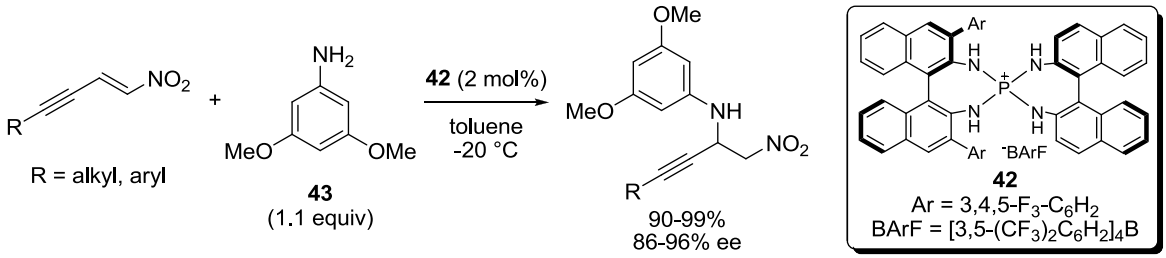
Scheme 15: Enantioselective ring opening of *meso*-aziridines with TMS-azide.

Aza-Michael additions to nitroalkenes represent another important method for 1,2-diamine synthesis. The *β*-nitroamine products may be easily converted to 1,2-diamines by simple reduction of the nitro group. Furthermore, due to the unique reactivity of the nitro group, these compounds may be converted to other important compounds such as *α*-aminoacids. Jørgensen *et al.* investigated the use of imines as ammonia equivalents in organocatalysed Michael additions to nitroalkenes.[33] Thiourea **40** successfully catalysed the Michael addition of benzophenone imine **41** to a variety of nitroalkenes in high yield and enantioselectivity (Scheme 16). Hydrolysis of the product imine could be performed in a one-pot fashion to unmask the free amine. Ooi and co-workers also recently demonstrated a highly enantioselective aza-Michael addition of 2,4-dimethoxyaniline (**43**) to a variety of nitroenynes catalysed by chiral arylaminophosphonium borate **42** (Scheme 17).[34] The synthesis of the unprotected diamine was demonstrated by reduction of the nitro group and

subsequent oxidative cleavage of the 2,4-dimethoxylphenyl group with ceric ammonium nitrate (CAN).

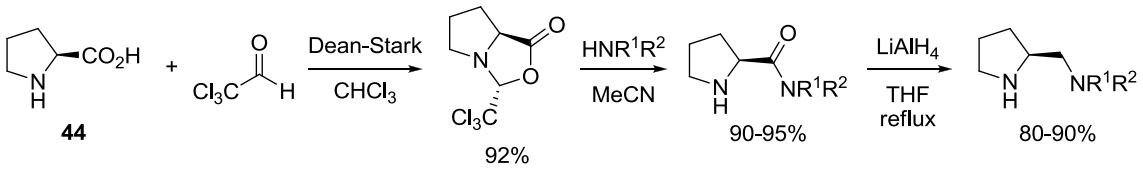


Scheme 16: Organocatalysed aza-Michael addition using ammonia equivalent **41**.



Scheme 17: Organocatalysed aza-Michael addition of 2,4-dimethoxyaniline (**43**).

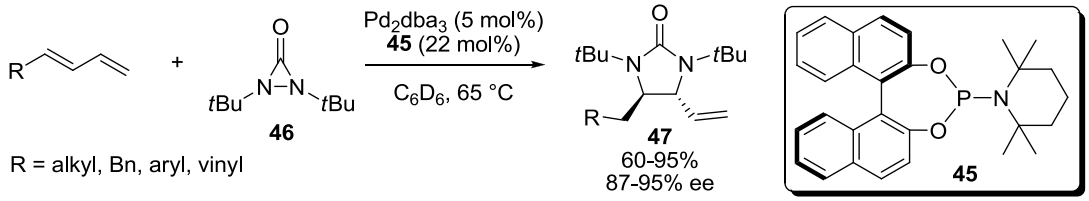
Another practical synthesis of 1,2-diamines is through the conversion of α-aminoacids. This method is attractive due to the availability of α-aminoacids, often in enantiopure form, which can be converted to 1,2-diamines by amide bond formation and reduction of the resulting amide.[1,7,35] This method was demonstrated by Amedjkouh who synthesised a variety of 1,2-diamines derived from (*S*)-proline (**44**) (Scheme 18).[35a]



Scheme 18: Synthesis of 1,2-diamines from α-aminoacids.

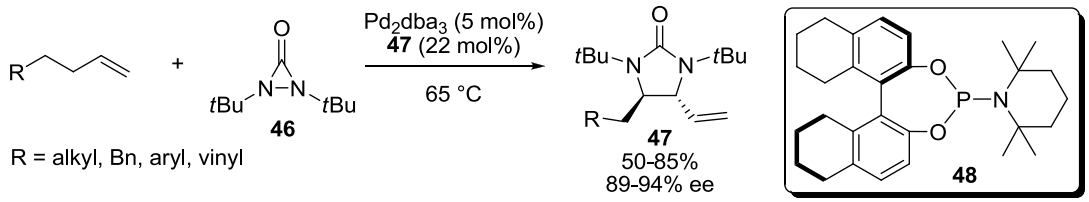
A more direct route to 1,2-diamines is the direct introduction of two nitrogen atoms onto an alkene (Figure 5, category 2). Diamination has until recently remained largely unexplored. This is in contrast to the extensively studied catalytic dihydroxylation and aminohydroxylation reactions that have established themselves as valuable tools for synthetic chemists.[36] Early examples involved the use of stoichiometric metal reagents so remained far less practical than dihydroxylation and aminohydroxylation protocols, even though stereoselective examples were reported using either chiral auxiliaries or chiral Lewis acids.[1,7,36] Recent advances have enabled direct diamination of alkenes by using

transition metal (TM) derivatives in catalytic amounts.[36] Shi *et al.* reported the enantioselective diamination of dienes and trienes using a Pd(0) catalyst, derived from phosphoramidite **45**, and di-*tert*-butyldiaziridinone (**46**). The cyclic urea products (**47**) were formed in excellent yield and enantioselectivity (Scheme 19). The group demonstrated that cleavage of the *tert*-butyl groups and the urea could be achieved in high yield by treatment with TFA followed by HCl.[37]



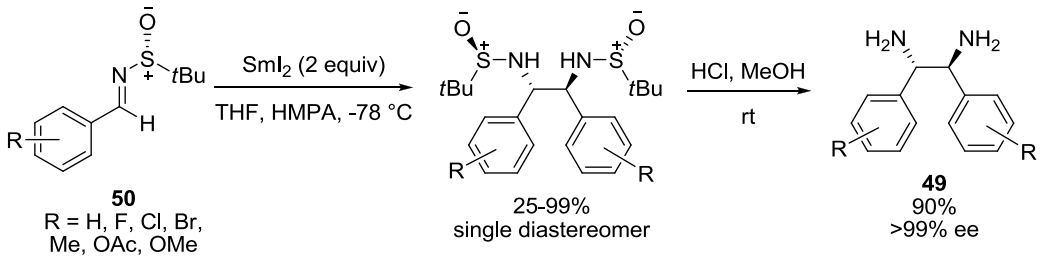
Scheme 19: Diamination catalysed by Pd(0)-phosphoramidite catalyst **45**.

The same group also demonstrated that the use of phosphoramidite ligand **48** under similar conditions enabled the diamination of allylic and homoallylic positions of terminal alkenes (Scheme 20).[38] Compared with the diamination of conjugated dienes, this formal C-H activation process offers the great advantage of using commercially available terminal alkenes, therefore eliminating the need to prepare conjugated dienes.



Scheme 20: Pd(0)-catalysed diamination of allylic and homoallylic positions of terminal alkenes.

A more convergent synthesis of 1,2-diamines is to take two nitrogen containing substrates and react them to form the C1-C2 bond of the diamine (Figure 5, category 3). One method that uses this mode of bond formation is the reductive coupling of imines. This method, however, is mainly only applicable to the synthesis of symmetric 1,2-diamines. Nonetheless, highly selective syntheses of 1,2-diamines using this method have been developed. These include a highly enantio- and diastereoselective synthesis of C_2-symmetric 1,2-diamines (**49**) by Xu *et al.* who used a SmI_2-mediated homocoupling of chiral *N-tert*-butylsulfinyl imines (**50**) (Scheme 21).[39]



Scheme 21: Reductive coupling of imines mediated by SmI_2.

Although the synthesis of C_2-symmetic 1,2-diamines is important, with the products finding application in a variety of asymmetric transformations (see section 1.2.2), more diverse methods that allow the selective synthesis of unsymmetrical 1,2-diamines would be very beneficial. One such method is the nitro-Mannich reaction, which will be discussed in the following section of this introductory chapter.

1.3 The Nitro-Mannich Reaction

The nitro-Mannich (or aza-Henry) reaction is one of a family of important C-C bond forming reactions consisting of the addition of active C-H nucleophiles to C=X bonds. Also included within this description are the well-known and extensively studied aldol, Mannich and Henry (or nitro-aldol) reactions (Figure 6).[40] The nitro-Mannich reaction, unlike the analogous members of this family of reactions, has received far less attention from researchers. Recently, however, there has been a great increase in the number of groups investigating this important reaction, resulting in the rapid development of new nitro-Mannich methodologies. An important feature of the nitro-Mannich reaction is the synthetic versatility of the *β*-nitroamine products, which are useful building blocks for the synthesis of structurally diverse 1,2-diamines and *α*-aminoacid derivatives. Although discovered well over a century ago, it was not until the first acyclic diastereoselective nitro-Mannich reaction was reported in 1998 that it began to receive significant attention.[41] Nitro-Mannich procedures are now available that allow the synthesis of a wide variety of *β*-nitroamines with high levels of diastereo- and enantioselectivity. The following section presents a review of the development of the nitro-Mannich reaction over the past 116 years.

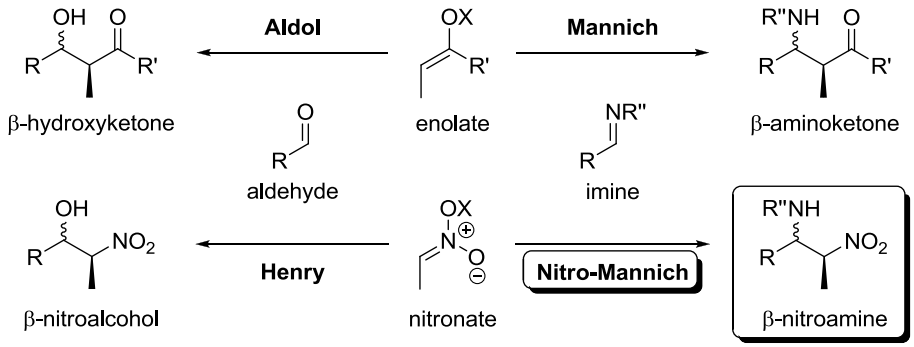
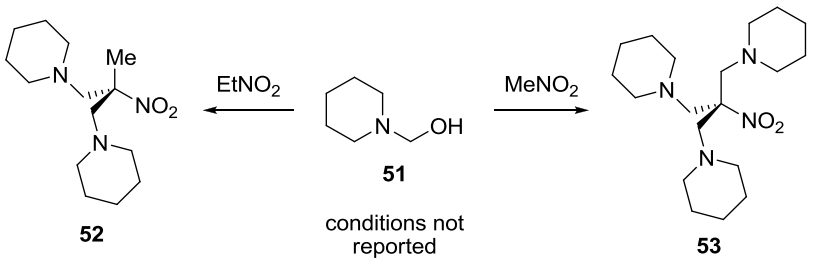


Figure 6: The addition of active C-H nucleophiles to C=X bonds.

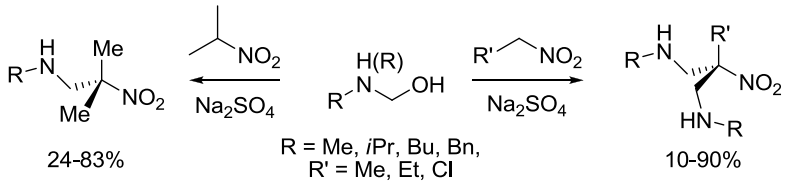
1.3.1 Pre-1998 Development

The first report of a nitro-Mannich reaction was by Henry in 1896.[42] He described the reaction of the hemi-aminal **51** derived from formaldehyde and piperidine with nitromethane and nitroethane to form the di- and tri-piperidines **52** and **53** (Scheme 22).



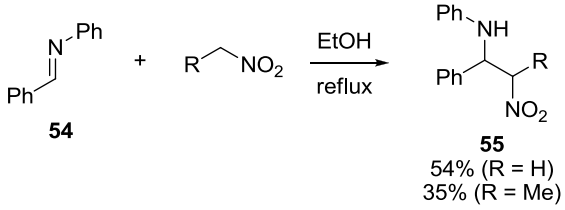
Scheme 22: The first reported nitro-Mannich reaction.

The next development came from Senkus and Johnson in 1946.[43] They reported the nitro-Mannich reaction between a number of nitroalkanes and hemi-aminals formed from formaldehyde and a variety of alkylamines (Scheme 23). The product nitroamines were then reduced by hydrogenation to form the corresponding polyamines. A few other similar nitro-Mannich reactions that utilised imines derived from formaldehyde were also reported in the mid-20th century.[44]



Scheme 23: Early development of the nitro-Mannich reaction.

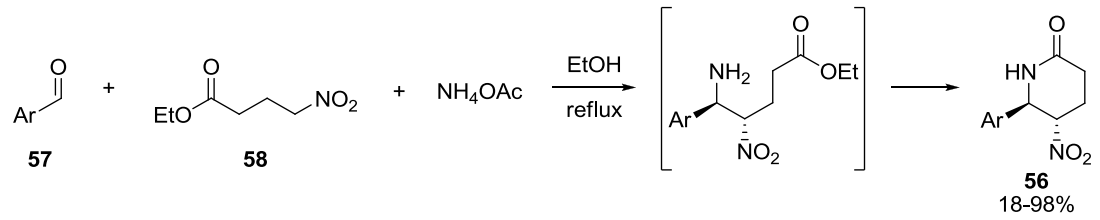
The first example of a nitro-Mannich reaction performed with a preformed imine was given by Hurd and Strong in 1950.[45] They successfully reacted nitromethane and nitroethane with benzylidineaniline (**54**) by refluxing in ethanol, forming the corresponding *β*-nitroamines **55** in moderate yields (Scheme 24).



Scheme 24: The first nitro-Mannich reaction with a pre-formed imine.

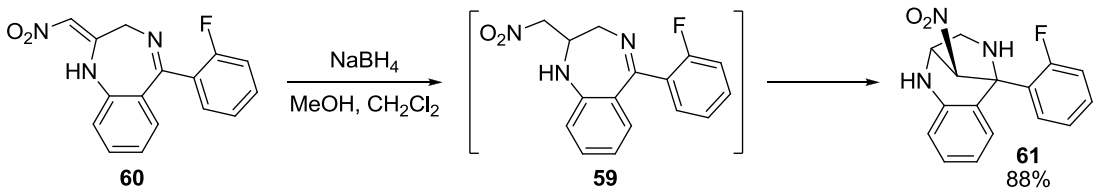
The use of the nitro-Mannich reaction in the synthesis of 5-nitropiperidin-2-ones (**56**) was later described by Jain and co-workers.[46] They performed a three component reaction cascade between a range of aromatic aldehydes (**57**), ethyl 4-nitrobutanoate (**58**) and

ammonium acetate (Scheme 25). The products, which were confirmed by ^{1}H NMR to possess *anti* stereochemistry, were formed in low to good yields.



Scheme 25: The first diastereoselective nitro-Mannich reaction.

There was also a report of an unexpected nitro-Mannich observed by Walser and co-workers during the synthesis of pharmacologically active benzodiazepines.[47] They observed the intramolecular nitro-Mannich reaction of nitro-imine **59**, formed from the $NaBH_4$ reduction of nitroalkene **60**. Nitroamine **61** was formed in 88% yield and the structure was confirmed by single crystal X-ray analysis (Scheme 26).



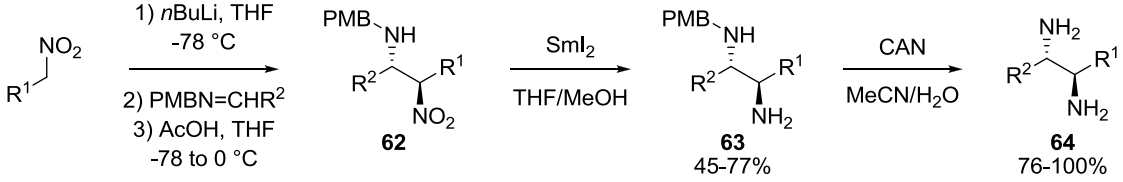
Scheme 26: Unexpected intramolecular nitro-Mannich reaction.

Few other examples of nitro-Mannich reactions were reported prior to 1998, which is surprising considering the extent to which the aldol, Mannich and Henry reactions have been developed over the last century. Nonetheless, since 1998 there has been a huge increase in the number of publications concerning the nitro-Mannich reaction. Today, methodologies have been developed that enable highly diastereo- and enantioselective reactions to be performed.

1.3.2 Non-Catalytic Reactions

The first acyclic diastereoselective nitro-Mannich reaction was reported by the Anderson group in 1998.[41] They revealed that deprotonation of nitroalkanes with *n*BuLi, forming a lithium nitronate, followed by introduction of an imine and acetic acid enabled the formation of *β*-nitroamines **62** in high yield and, in certain cases, high diastereoselectivity (Scheme 27). The majority of substrates used gave good *anti*-selectivity, which was

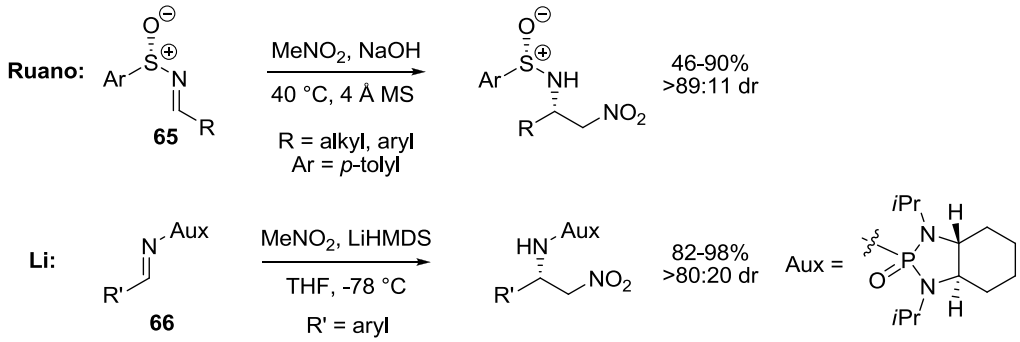
proposed to arise from the reaction proceeding through a Zimmerman-Traxler-type chair transition state. Due to the instability of *β*-nitroamines **62** the group went on to synthesise the corresponding 1,2-diamines **63** by reduction of the nitro group. Removal of the amine protecting group furnished the bis-primary amines **64**. The presence of acetic acid was found to be crucial for the nitro-Mannich reaction to occur. This is because the addition of a nitronate anion to an imine is thermodynamically disfavoured due to the difference in pK_a values between the nitronate (pK_a 9) and the aza-anion product (pK_a 35). This report represented an important turning point for the development of the nitro-Mannich reaction as it provided a method for the reliable formation of *β*-nitroamines with high levels of diastereoselectivity and demonstrated that they could be converted easily into 1,2-diamines.



R^1 = Et, Me_2, Ph; R^2 = Ph, *n*Pentyl, Cy, CH_2OBn, $(CH_2)_3Ph$

Scheme 27: The first acyclic diastereoselective nitro-Mannich reactions.

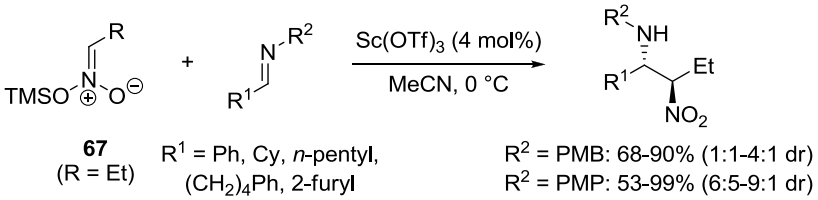
The same group later reported an improvement to this nitro-Mannich protocol by replacing the PMB-protected imines with OMB-protected imines. Using the OMB-protected imines led to improved yields and higher substrate scope for the reaction.[48] Other notable non-catalytic nitro-Mannich reactions reported since 1998 include several asymmetric protocols that make use of imines bearing a chiral auxiliary. Ruano and Cid applied chiral *N*-*p*-tolylsulfinylimines (**65**) in highly diastereoselective NaOH-mediated nitro-Mannich reactions,[49] whereas Li *et al.* used chiral *N*-phosphinoyl imines (**66**) derived from 1,2-diaminocyclohexane in LiHMDS-mediated reactions (Scheme 28).[50]



Scheme 28: Auxiliary controlled nitro-Mannich reactions.

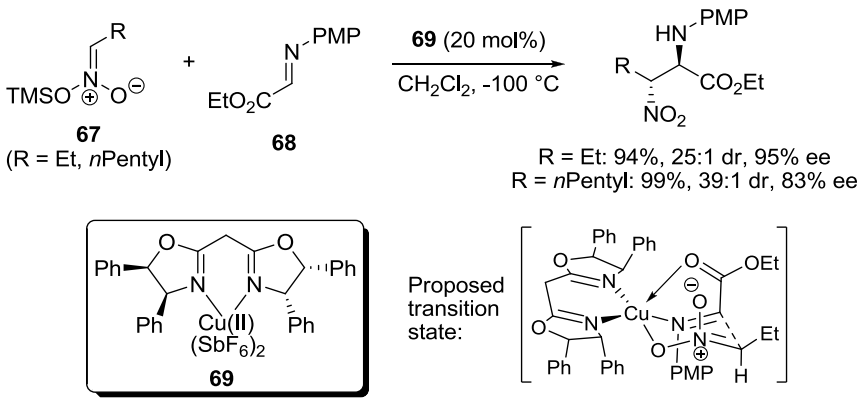
1.3.3 Indirect Metal-Catalysed Reactions

In 2000, the Anderson group published the first indirect nitro-Mannich reaction.[51] The communication detailed their preliminary results in the development of an asymmetric nitro-Mannich reaction, in which they planned to utilise TMS-nitronates (**67**) in Lewis acid catalysed reactions. The use of Lewis acids in the nitro-Mannich reaction of lithium-nitronates only gave acceptable yields when stoichiometric quantities of Lewis acid were used. This was suggested to be a result of the product aza-anion binding too tightly to the Lewis acid. The use of TMS-nitronates allowed the use of catalytic quantities of Lewis acid, thereby providing the opportunity to use a chiral ligand to induce asymmetry into the reaction. The group found $Sc(OTf)_3$ to be an effective Lewis acid for the reaction of TMS-nitronates (**67**) with a number of alkyl and aryl imines (Scheme 29). The use of PMP-imines was found to give increased diastereoselectivity and yield in several cases. In a later publication, the same group expanded the substrate scope of this reaction and also provided similarly successful procedures catalysed by $Cu(OTf)_2$ and $Ti(OiPr)_4$.[48]



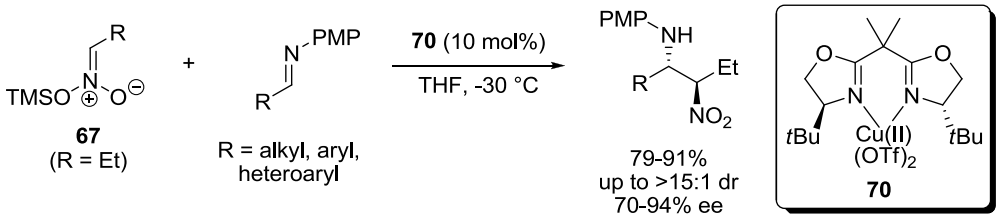
Scheme 29: Lewis acid catalysed nitro-Mannich reaction.

The following year, the group of Jørgensen published the first asymmetric nitro-Mannich reactions of TMS-nitronates with ethylglyoxylate-imine **68** (Scheme 30).[52] They used a Cu(II)-catalyst with *cis*-DiPh-BOX ligand **69**, to achieve excellent yields, enantio- and diastereoselectivities. The communication gives several examples to demonstrate the scope of the reaction with respect to the TMS-nitronate but appears to be limited to imines derived from ethylglyoxylate. They account for the stereochemical induction by proposing a mechanism that involves binding of the *α*-iminoester to the catalyst in a bidentate fashion followed by coordination of the TMS-nitronate to the copper centre. The necessary presence of the ester group, and the requirement that the reaction is performed at -100 °C, severely limits the synthetic utility of this method.



Scheme 30: Asymmetric Lewis acid catalysed nitro-Mannich reaction.

In 2005, the Anderson group reported an improved procedure that used a lower catalyst loading and demonstrated a broad substrate scope with respect to the imine used.[53] The use of Cu(II)-*t*Bu-BOX catalyst **70** promoted the nitro-Mannich reactions to form a range of *β*-nitroamines in excellent yield, diastereo- and enantioselectivities (Scheme 31). They demonstrated that the use of imines capable of bidentate coordination to the catalyst (such as OMB-imines) prevented the bidentate coordination of the chiral ligand, thereby compromising the stereoinducing effect. The use of PMP-imines (only capable of monodentate binding to the catalyst) greatly enhanced the stereoselectivity of the reaction.

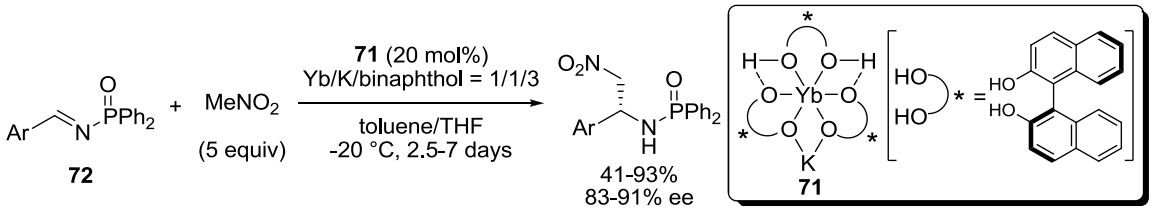


Scheme 31: Asymmetric Lewis acid catalysed nitro-Mannich reaction.

1.3.4 Direct Metal-Catalysed Reactions

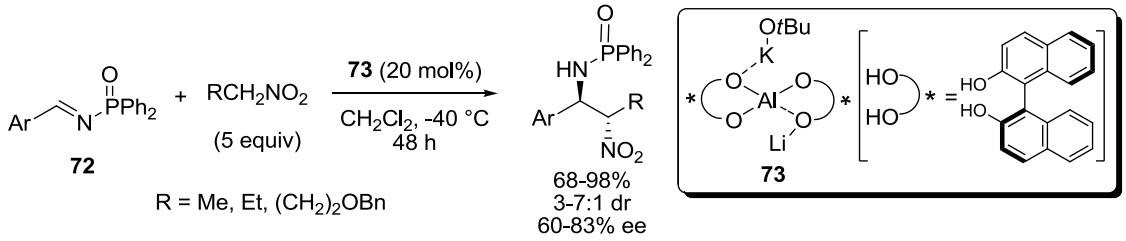
Although the indirect metal-catalysed nitro-Mannich reactions provide efficient access to *β*-nitroamines in high yield and stereoselectivity, the requirement to preform the silyl-nitronates limits its synthetic utility. A more attractive method would allow the direct coupling of nitroalkanes with imines *via in situ* nitronate formation. The first example of an asymmetric direct metal-catalysed nitro-Mannich reaction was reported by Shibasaki *et al.* in 1999.[54] They used the Yb/K heterobimetallic complex **71**, which contains both Lewis acidic and Brønsted basic sites, for the reaction between nitromethane and a variety of

aryl-phosphinoylimines (**72**) (Scheme 32). The catalyst successfully promoted the nitro-Mannich reaction in excellent enantioselectivities, however, several limitations exist. These include the long reaction times, the requirement for the slow addition of nitromethane for optimal selectivity, the use of 60 mol% of the chiral ligand, and the failure of the catalyst to promote the nitro-Mannich reaction of higher homologues of nitromethane, such as nitroethane.



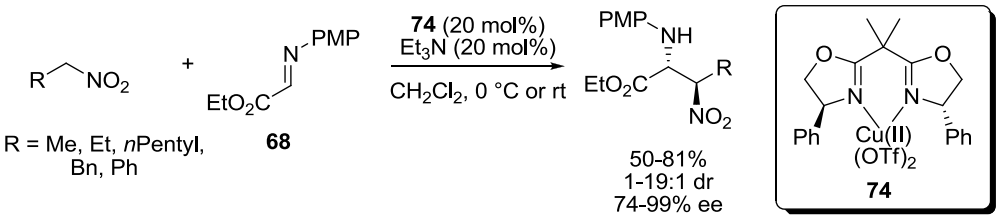
Scheme 32: Direct nitro-Mannich reactions catalysed by Yb/K/binaphthoxide-catalyst **71**.

In 2001, the same group reported the use of Al/Li/binaphthoxide-KO*t*Bu catalyst **73** to promote the reaction of larger nitroalkanes with aryl-phosphinoylimines **72** (Scheme 33).[55] The larger binding pocket of **73** compared to **71** was proposed to be responsible for the increased reactivity with larger nitroalkanes. The *β*-nitroamines were formed in excellent yield and good diastereo- and enantioselectivity.



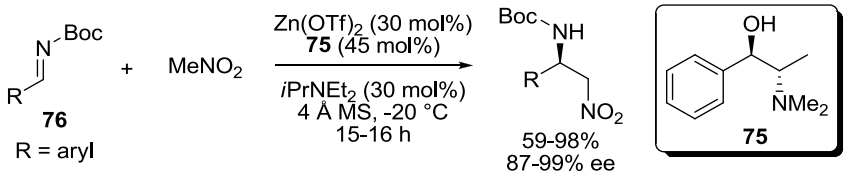
Scheme 33: Direct nitro-Mannich reactions catalysed by Al/Li/binaphthoxide-KO*t*Bu catalyst **73**.

In the same year, Jørgensen *et al.* reported an improved method for their Cu(II)-*cis*-DiPh-BOX (**69**)-catalysed nitro-Mannich reaction of TMS-nitronates (Scheme 30).[56] The use of TMS-nitronates was avoided through the use of catalytic amounts of organic base in the reaction. They used catalyst **74** with catalytic triethylamine to promote the direct nitro-Mannich between a variety of nitroalkanes and *α*-iminoester **68** (Scheme 34). The reaction gave moderate to good yields and stereoselectivities, however, only imine **68** was compatible with the reaction conditions, therefore, limiting its substrate scope.



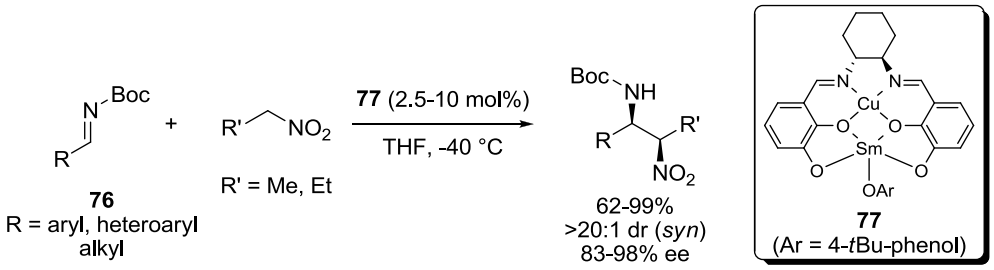
Scheme 34: Direct nitro-Mannich reaction catalysed by Et_3N and Cu(II)-Ph-BOX **74**.

Palomo *et al.* reported the use of a much simpler cooperative catalyst system consisting of *N*-methylephedrine (**75**), Hünig's base and $Zn(OTf)_2$.[57] This catalysed the reaction between nitromethane and a number of *N*-Boc-aryl-imines (**76**) giving the products with high enantioselectivities (Scheme 35). The authors failed to report the nitro-Mannich reaction with any nitroalkanes other than nitromethane and also high catalyst loadings were required to achieve good selectivities, making this method of limited practicability.



Scheme 35: $Zn(OTf)_2$/*N*-methylephedrine-catalysed direct nitro-Mannich reaction.

The most successful direct metal-catalysed nitro-Mannich reaction to date is an improved procedure from the group of Shibasaki.[58] Through the use of heterobimetallic Cu-Sm-Schiff base complex **77** the group were able to perform highly *syn*-selective nitro-Mannich reactions between a range of *N*-Boc-aryl-imines (**76**) and nitroethane and nitropropane (Scheme 36). The *syn*-*β*-nitroamines were obtained in excellent yield and enantio- and diastereoselectivities. The excellent *syn*-selectivities obtained from this method are in stark contrast to all previously reported methods, and most published since, which are generally highly selective for the *anti*-diastereomer. The authors carried out extensive mechanistic studies to determine the active catalyst to be a trimeric form of catalyst **77**. Cooperative dual activation of both the nitroalkane and imine by Sm and Cu are crucial for the *syn*-selectivity. The Sm-aryl oxide moiety in the catalyst acts as a Brønsted base to generate a Sm-nitronate, while the Cu(II) acts as a Lewis acid to control the position of the Boc-imine. The group proposes the reaction to proceed *via* sterically less hindered **TS-1**, which would be favoured over **TS-2**, to give the *syn*-product upon protonation with 4-*t*Bu-phenol (Figure 7).



Scheme 36: Heterobimetallic Cu-Sm-Schiff base (**77**) catalysed *syn*-selective nitro-Mannich reaction.

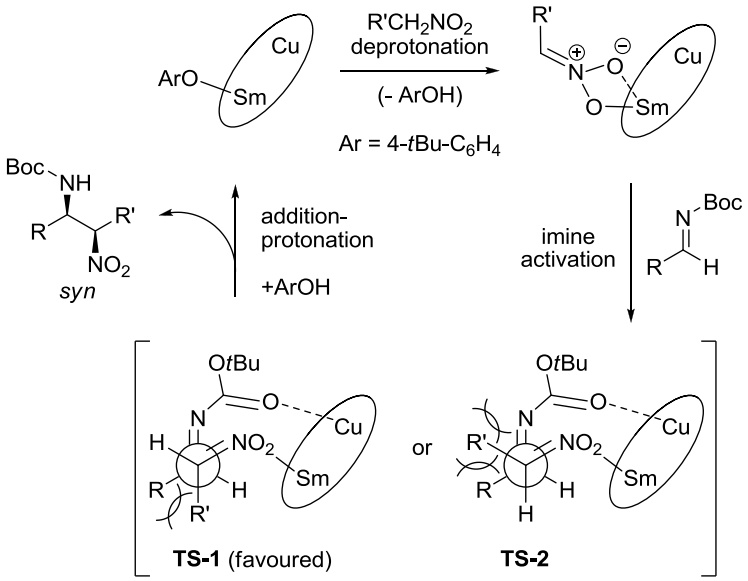
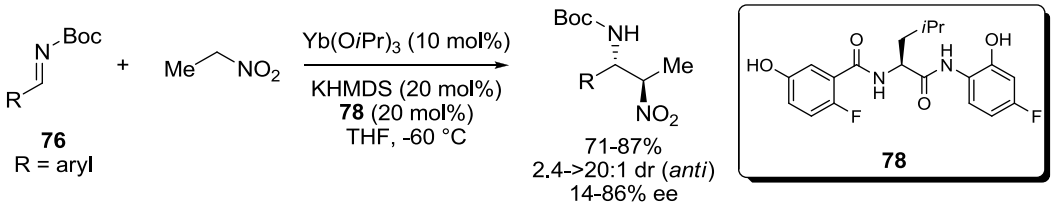


Figure 7: Proposed mechanism of Shibasaki's *syn*-selective nitro-Mannich reaction.

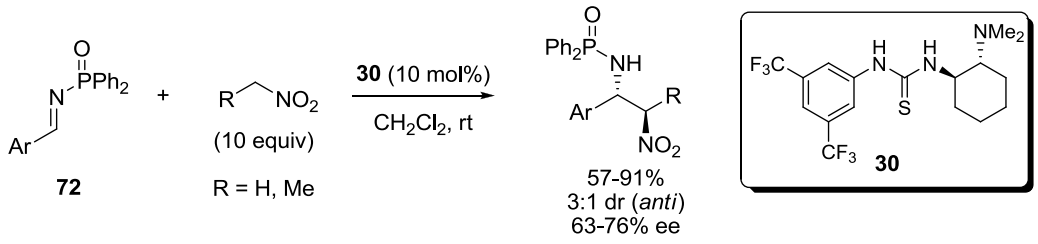
The same group also published an analogous *anti*-selective nitro-Mannich using a heterobimetallic catalyst derived from amide **78**.[59] Although the yields and diastereoselectivities were good, the enantioselectivities failed to match those of their *syn*-selective protocol (Scheme 37).



Scheme 37: Heterobimetallic Yb/K/amide (**78**)-catalysed *anti*-selective nitro-Mannich reaction.

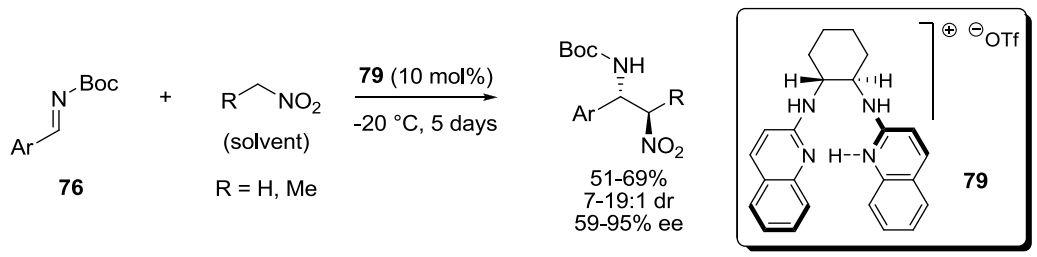
1.3.5 Organocatalytic Reactions

Since the introduction of the field of organocatalysis it has been applied to a broad range of asymmetric reactions. Consequently, a number of different organocatalysts have been developed for use in asymmetric nitro-Mannich reactions. The first asymmetric organocatalysed nitro-Mannich reaction was reported by the group of Takemoto in 2004.[25a] The group applied thiourea catalyst **30**, which they had previously developed for use in asymmetric Michael additions,[24a] to the reaction of nitromethane with a range of aryl-phosphinoylimines **72** (Scheme 38). The reactions were high yielding but only gave moderate enantioselectivities. Only a single diastereoselective example was given by using nitroethane to form the product in a modest 3:1 dr in favour of the *anti*-diastereomer.



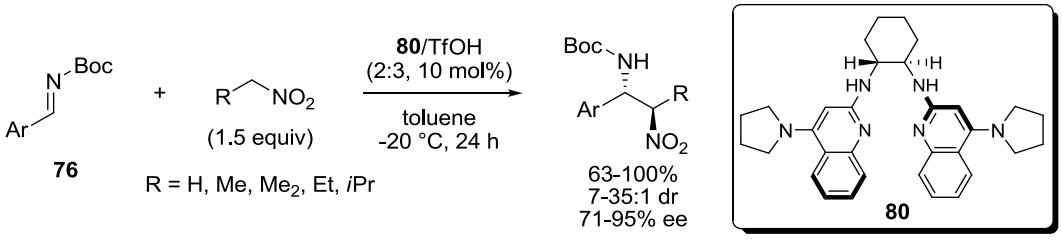
Scheme 38: The first asymmetric organocatalytic nitro-Mannich reaction.

Less than a week after the initial report by Takemoto in 2004, Johnston *et al.* published the use of an alternative organocatalytic nitro-Mannich reaction.[60a] They implemented the use of chiral proton catalyst **79** for the enantio- and diastereoselective nitro-Mannich reaction of *N*-Boc-aryl-imines **76** with nitromethane and nitroethane (Scheme 39). They speculate that the bis-amidine ligand sequesters the proton from solvent interactions, thereby preventing achiral solvent-coordinated Brønsted acid catalysis, to create a chiral proton coordination complex capable of inducing enantioselectivity. The method, however, suffered from long reaction times and only demonstrated limited substrate scope as it required the use of electron-poor aryl-imines to achieve high enantioselectivities. Furthermore, the use of the nitroalkane as the solvent limits the applicability of this method to more complex nitroalkanes.



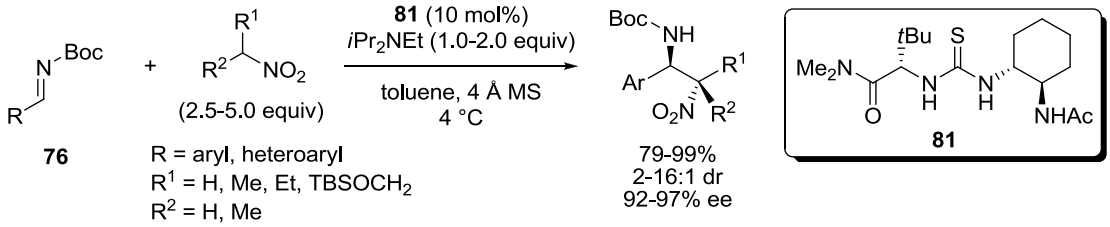
Scheme 39: Enantioselective chiral proton-catalysed nitro-Mannich reaction.

Johnston *et al.* later reported the use of bis-amidine catalyst **80**, which demonstrated improved efficiency in nitro-Mannich reactions.[60b] The reactions with the new catalyst system gave higher yields and stereoselectivities over a wide range of imines, and several nitroalkanes, and were complete in 24 h using just 1.5 equivalents of nitroalkane. They rationalise that the increased Brønsted basicity of **80** (compared to **79**) is responsible for the increased reactivity of the catalyst. They also uncovered an interesting effect caused by the amount of TfOH used in the reaction and found that a 2:3 ratio of **80**:TfOH provided the optimum yield and stereoselectivity (Scheme 40).



Scheme 40: Improved chiral proton-catalysed nitro-Mannich reaction.

In 2005, Jacobsen *et al*. demonstrated the use of thiourea catalyst **81** as a very efficient catalyst for the nitro-Mannich reaction between nitroethane and *N*-Boc-aryl-imines **76** (Scheme 41).[61] Although the yields and stereoselectivities were comparable to those obtained using Takemoto's protocol, the lack of a basic functionality in the catalyst required the addition of an equivalent of a tertiary amine base for the reaction to reach completion.



Scheme 41: Jacobsen's thiourea-catalysed nitro-Mannich reaction.

Inspired by the excellent results achieved by the groups of Johnston and Jacobsen when using *N*-Boc-aryl-imines **76** (see schemes 39 and 41), Takemoto's group later reported an improvement to their thiourea-catalysed method (see Scheme 38) by using *N*-Boc-imines **76**.[25b] While still using catalyst **30**, changing from phosphinoyl-imines **72** to *N*-Boc-imines **76** enabled the *β*-nitroamines to be formed in much higher enantioselectivities. They also demonstrated an improved scope of the reaction with respect to the nitroalkane used, with good to excellent diastereoselectivities achieved for a range of functionalised nitroalkanes. Their proposed mechanism proceeds *via* ternary complex **82** consisting of the imine and nitronate coordinated to the thiourea and tertiary amino group of catalyst **30** by hydrogen bonding. The thiourea moiety functions both to activate the *N*-Boc-imine (as shown in **82**) and also to aid in the deprotonation of the nitroalkane (Figure 8).

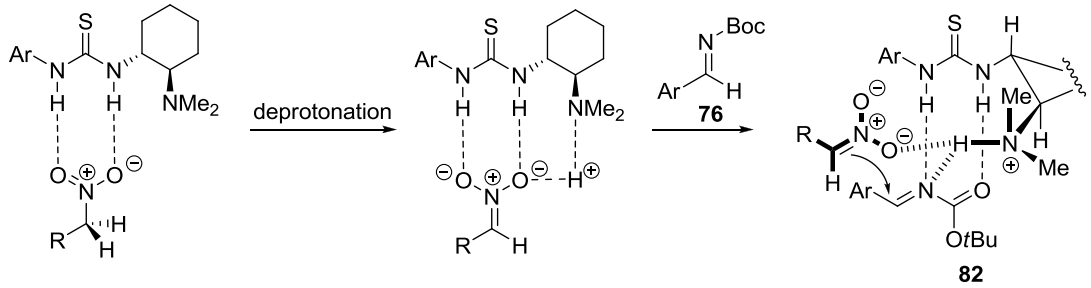
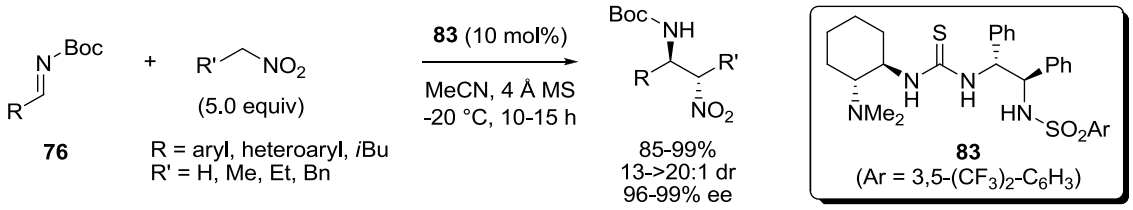


Figure 8: Proposed mechanism of Takemoto's thiourea-catalysed nitro-Mannich reaction.

Since the reports by Takemoto and Jacobsen on the application of thiourea-based organocatalysts to asymmetric nitro-Mannich reactions, there have been a large number of publications from other groups demonstrating the use of thioureas bearing various chiral scaffolds. These include catalysts derived from cinchona alkaloids,[62] chiral sulfonamides,[63] glycosides[64] and steroids.[65] These have not all been discussed in this thesis, however, two examples of interest have been detailed below.

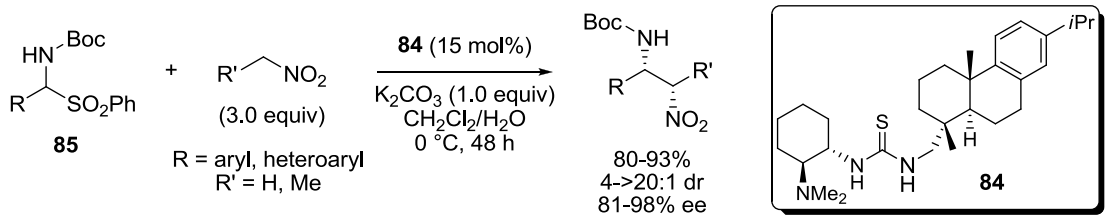
The most efficient organocatalytic nitro-Mannich protocol reported to date was presented by C. Wang *et al* in 2008.[66] They used chiral thiourea **83** to catalyse the nitro-Mannich reaction between a range of *N*-Boc-imines **76** and a number of nitroalkanes (Scheme 42). Near quantitative yields were obtained in the majority of cases, accompanied by exceptional stereoselectivities. The conditions were also found to have a high tolerance for alkyl imines, demonstrated by the use of the *N*-Boc-imine derived from *iso*-butyraldehyde which gave comparable yields and selectivities to aryl-imines. This methodology represents

the best *anti*-selective organocatalytic nitro-Mannich reaction reported so far and is complementary to the highly *syn*-selective heterobimetallic Cu-Sm-Schiff base complex-catalysed reaction reported by Shibasaki (see Scheme 36).[58]



Scheme 42: Wang's thiourea-catalysed nitro-Mannich reaction.

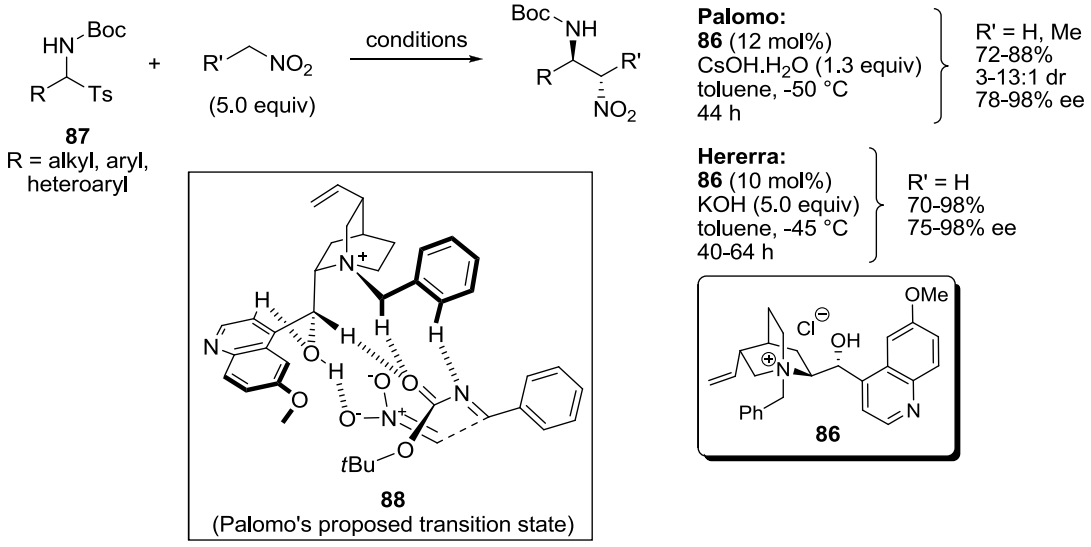
In 2009, R. Wang *et al.* published the only report of an asymmetric *syn*-selective organocatalytic nitro-Mannich reaction.[65] They used the rosin-derived thiourea **84** in the reaction of nitromethane and nitroethane with *N*-Boc-imines formed *in situ* from *α*-amidosulfones **85** (Scheme 43). They found that the use of a biphasic (water/dichloromethane) solvent system was crucial for achieving high enantioselectivity. The group also demonstrated that the 1,2-diaminocyclohexane group in the catalyst was responsible for the stereochemical control as switching to the (*R*)-enantiomer provided efficient reversal of selectivity in the nitro-Mannich reaction. The reaction gave excellent yields and enantioselectivities when nitromethane was used. Several examples of reactions with nitroethane demonstrated that high selectivity for the *syn*-diastereomers was obtained. The authors, however, failed to elaborate on this remarkably high *syn*-selectivity and offered no explanation for the observed diastereoselectivity.



Scheme 43: *Syn*-selective thiourea-catalysed nitro-Mannich reaction.

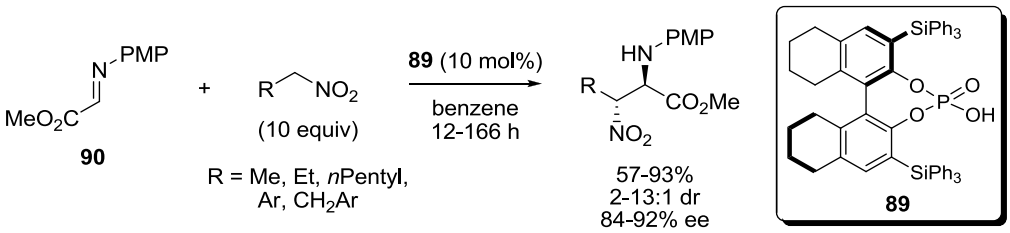
Various other types of organocatalysts have also been applied to nitro-Mannich reactions. The groups of Palomo and Hererra independently reported the use of cinchona-derived phase-transfer-catalyst **86** in the nitro-Mannich reaction of *α*-amidosulfones **87** with nitroalkanes.[67a,68] Both groups gave near identical conditions, with the exception of the

inorganic base used for the *in situ* formation of the *N*-Boc-imines from the *α*-amidosulfones, forming the *β*-nitroamine products in excellent yields and enantioselectivities (Scheme 44). The method is particularly useful for imines derived from enolisable aldehydes as the formation of the *N*-Boc-imines *in situ* avoids the need to isolate these unstable substrates. Herrera also demonstrated that the method was not restricted to Boc-protected substrates and could be extended to other carbamoyl protecting groups such as Cbz. However, Herrera failed to give any examples of reactions involving higher order nitroalkanes, whereas Palomo reported reactions with nitroethane giving moderate to high *anti*-selectivity. Palomo went on to give a detailed mechanistic study of this nitro-Mannich reaction.[67b] Through the use of computational methods to calculate the energy levels of the possible transition states they proposed that the mechanism proceeds *via* transition state **88** (Scheme 44). A hydrogen bonding network creates a stable complex resulting in high enantioselectivity. This consists of a hydrogen bond between the O-H of the catalyst and the nitronate anion, which was confirmed by the drastically lower reactivity of catalysts bearing protected alcohols, and three additional hydrogen bonds between the carbamate of the imine and a number of C-H bonds of the catalyst. Binding of the imine in this orientation, with the *tert*-butyl group orientated away from the catalyst's bicycle, results in nucleophilic attack of the nitronate from the *Si* face of the imine. The authors did not offer any explanation for the high *anti*-diastereoselectivity obtained with higher order nitroalkanes.



Scheme 44: Phase-transfer-catalysed nitro-Mannich reactions and proposed transition state.

Rueping *et al.* described the first organocatalytic Brønsted acid-catalysed nitro-Mannich reaction of *α*-iminoesters.[69] They were able to use the BINOL-derived phosphoric acid **89** to catalyse the reaction of a variety of nitroalkanes with *α*-iminoester **90** (Scheme 45). The yields were good to excellent and the products were obtained in high enantio- and diastereoselectivity in favour of the *anti*-product. The protocol offers very good nitroalkane scope, however, the large excess required (10 equiv) limits the practicability of this method if more complex nitroalkanes were required. Furthermore, the procedure suffers from long reaction times and has only been applied to the reaction of a single imine.

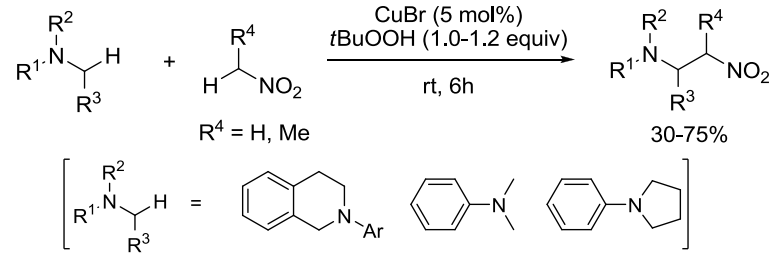


Scheme 45: Chiral phosphoric acid-catalysed nitro-Mannich reaction.

1.3.6 Miscellaneous Reactions

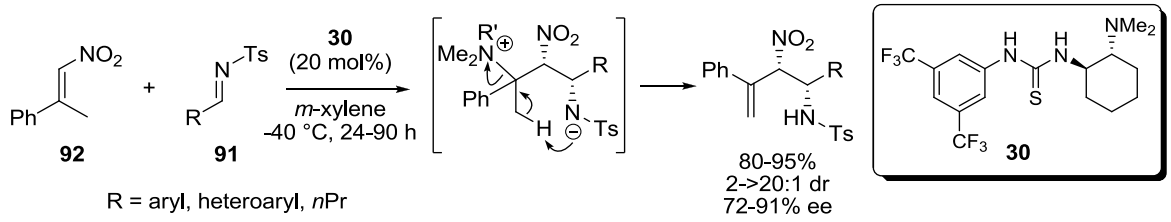
The nitro-Mannich reactions that have been described so far in this thesis have applied to the direct synthesis of *β*-nitroamines using a 'classical' nitro-Mannich reaction, that being the direct reaction of nitroalkanes/nitronates with imines, or imine precursors. There are, however, a number of other 'non-classical' methodologies that have been developed. These include a number of tandem or cascade reactions. They make use of the nitro-Mannich reaction either as the first step in the cascade or as a subsequent step only made possible due to the *in situ* formation of the nitroalkane or imine coupling partner. These types of reactions enable greater levels of structural diversity to be achieved in fewer synthetic steps and from simpler starting materials.

There have been several studies on dehydrogenative cross coupling reactions of amines and nitroalkanes.[70] The first use of this methodology for nitro-Mannich reactions was reported by Li *et al.* in 2005.[70a] They used a simple Cu(I)-catalyst in combination with *tert*-butylhydroperoxide to achieve cross-dehydrogenative-coupling reactions between a number of cyclic and acyclic tertiary amines and simple nitroalkanes to form *β*-nitroamines in moderate to good yields (Scheme 46).



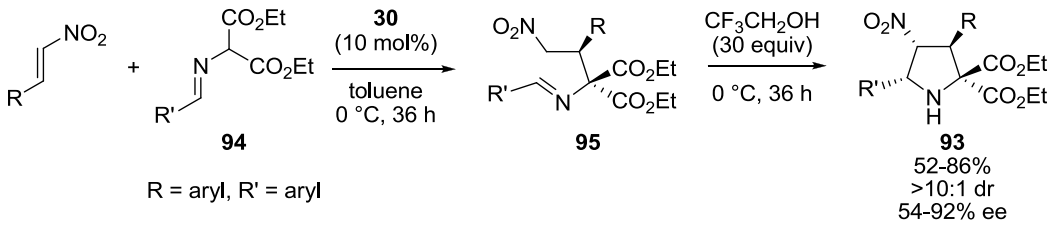
Scheme 46: Cross-dehydrogenative-coupling reactions of tertiary amines and nitroalkanes.

Another example of a 'non-classical' nitro-Mannich reaction was reported by Xu *et al.*[71] They used Takemoto's thiourea catalyst **30** in highly enantio- and diastereoselective aza-Morita-Baylis-Hillman reactions (Scheme 47). Excellent yields and selectivities were obtained for the reaction of a number of *N*-tosyl-imines **91** with nitroalkene **92**. The mechanism was proposed to proceed *via* an intramolecular proton shift in the *β*-elimination of the catalyst. The reactions were highly selective for the *syn*-diastereomers (confirmed by X-ray crystal analysis), however, no explanation of the origin of selectivity was given.



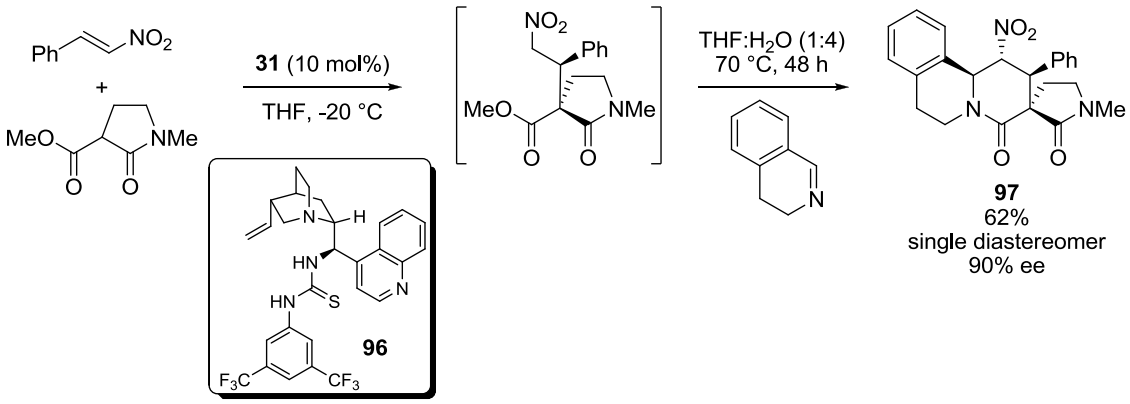
Scheme 47: Aza-Morita-Baylis-Hillman reaction.

Another tandem reaction that begins with a conjugate addition to a nitroalkene is the formal [3+2] cycloaddition of azomethine ylides with nitroalkenes. Takemoto *et al*. disclosed a highly enantio- and diastereoselective organocatalysed synthesis of pyrrolidines **93**.[72] The reaction proceeds in a step-wise manner consisting of Michael addition and subsequent nitro-Mannich reaction. They used thiourea catalyst **30** for the reaction of a variety of *α*-amino-malonate imines **94** with a number of nitroalkenes (Scheme 48). They found that the Michael addition proceeded well in toluene to give Michael adduct **95** but the addition of 2,2,2-trifluoroethanol to the reaction was required to affect the desired nitro-Mannich reaction. They found that the thiourea catalyst facilitated the stereocontrol in both the Michael addition and intramolecular nitro-Mannich reactions, providing the products in very high diastereoselectivities.



Scheme 48: Formal [3+2] cycloaddition of azomethine ylides with nitroalkenes.

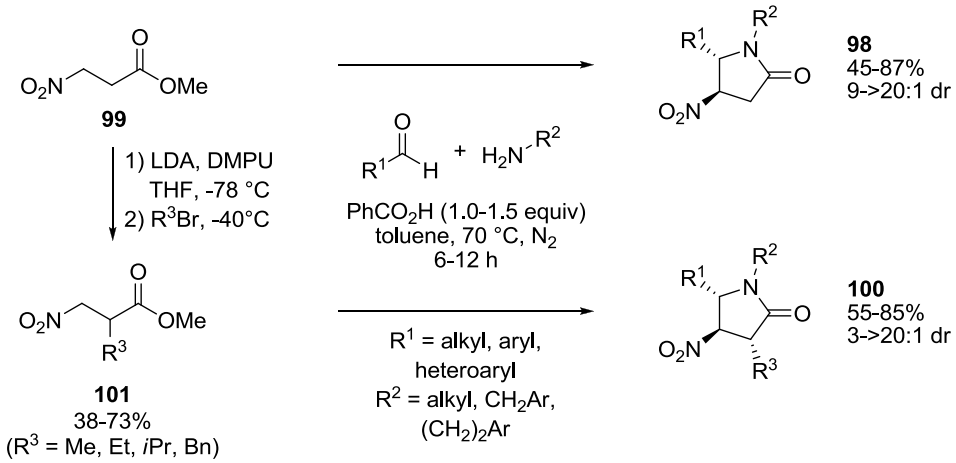
As was mentioned earlier, Jain *et al.* reported the synthesis of 5-nitropiperidin-2-ones using a nitro-Mannich/lactamisation cascade (see Scheme 25).[46] Although this reaction had been known for over 30 years, further development was not reported until Dixon *et al.* disclosed their synthesis of 3-nitropiperidinones in 2008.[73] The group were able to use *γ*-nitroesters, formed by Michael additions of malonates to nitroalkenes, in nitro-Mannich/lactamisation cascades with a variety of cyclic imines. The use of water as the solvent was found to be crucial to obtain high yields for the reaction. They went on to demonstrate that a one-pot asymmetric Michael addition-nitro-Mannich/lactamisation could be performed. Using thiourea **96** to catalyse the Michael addition, followed by introduction of the imine and water generated polycyclic lactam **97** in high yield and excellent enantio- and diastereoselectivity (Scheme 49). The same group also demonstrated that this reaction worked well for imines formed *in situ* from formaldehyde and benzylamine, which they successfully applied to a formal synthesis of (3*S*, 4*R*)-paroxetine.[74]



Scheme 49: Piperidinone synthesis using a nitro-Mannich/lactamisation cascade.

Dixon's group later expanded this methodology to the synthesis of pyrrolidinones **98** by utilising methyl-3-nitropropanoate (**99**) and a variety of *in situ* formed alkyl and aryl imines in nitro-Mannich/lactamisation cascade reactions.[75] Unlike when forming the piperidinones, no reaction occurred using water as a solvent. The optimal conditions were found to be with

degassed toluene, under an atmosphere of N_2 and with an equivalent of benzoic acid. A wide variety of aldehydes and amines were shown to be tolerated, with pyrrolidinones **98** being formed in moderate to good yield and excellent diastereoselectivity (Scheme 50). The reaction was also applicable to cyclic imines but the stereoselectivities were found to be lower. The synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones **100** was also achieved by alkylating **99**, forming **101**, prior to the nitro-Mannich/lactamisation cascade (Scheme 50).[75b] Alkylation prior to the nitro-Mannich/lactamisation was found to be necessary to introduce functionality alpha to the carbonyl as all attempts to alkylate **98** failed.



Scheme 50: Pyrrolidinone synthesis using a nitro-Mannich/lactamisation cascade.

1.4 Synthetic Utility of *β*-Nitroamines

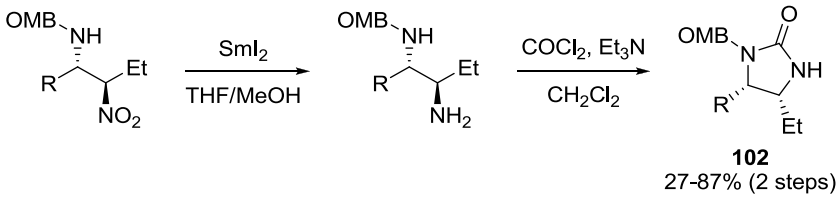
As was previously mentioned, one of the attractive features of the nitro-Mannich reaction is the straightforward synthesis of *β*-nitroamines. These versatile compounds can be converted into a number of useful products including 1,2-diamines (nitro reduction) and *α*-aminocarbonyls (Nef reaction). The following section will detail some examples of such transformations that have successfully demonstrated the utility of *β*-nitroamines generated *via* the nitro-Mannich reaction, including the application to the synthesis of complex natural products and pharmaceuticals.

1.4.1 Reduction to 1,2-Diamines

The most useful transformation of *β*-nitroamines is the reduction of the nitro group to form 1,2-diamines, which are, as was described in section 1.2, an important component of many biologically active compounds, organocatalysts and ligands used in asymmetric catalysis. The reduction of nitro groups has been well documented in the literature, mainly because nitration and subsequent reduction is the most important method for the preparation of aromatic amines. Consequently, the majority of cases concern the reduction of aromatic nitro groups. The reduction of aliphatic nitro groups is not always as straightforward as that of their aromatic counterparts. This is due to the slower rate of reduction and the possibility of cleavage of the C-N bond.[76] Further complications arise when reducing *β*-nitroamines as they are often susceptible to retro-addition. Nonetheless, successful reductions of the *β*-nitroamine products of nitro-Mannich reactions have been reported, making use of a range of different reduction protocols.

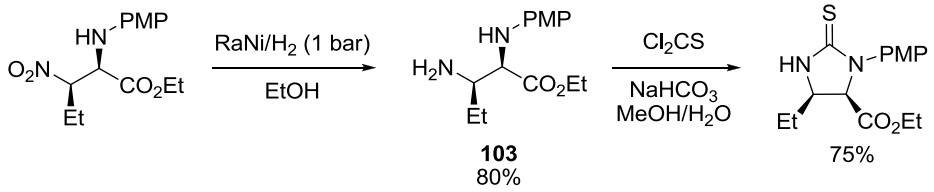
The first report of a reduction of *β*-nitroamines formed using a nitro-Mannich reaction was by Senkus and Johnson in 1946.[43] They used high pressure (34 bar) catalytic hydrogenation over Raney nickel to reduce nitroamines to the corresponding polyamines. Recent advances have provided much milder reducing conditions capable of tolerating a range of functional groups. In the paper by Anderson *et al*. detailing the first acyclic diastereoselective nitro-Mannich reactions the reduction of the nitro-Mannich products was performed using a single electron transfer reduction promoted by SmI_2 (see scheme 27),[41] a method originally reported by Sturgess *et al*. for the reduction of *β*-nitroamines formed from aza-Michael

additions to nitroalkenes.[77] This method was successfully used by the same group in the synthesis of cyclic ureas **102** (Scheme 51).[48,51] The group of Shibasaki also successfully used this SmI_2 reduction protocol.[54]



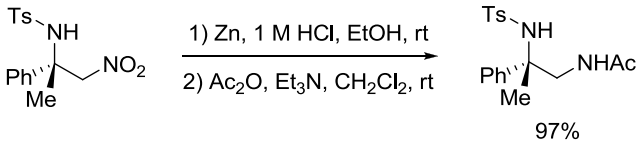
Scheme 51: SmI_2 reduction and cyclic urea formation.

Jørgensen *et al.* reported the Raney nickel catalysed hydrogenation of *β*-nitroamines in the synthesis of *α,β*-diaminoacid derivative **103**.[52] The reaction was performed under much milder conditions than those reported by Senkus and Johnson to obtain **103** in 80% yield without any loss of enantioselectivity (Scheme 52). Shibasaki also reported high yields using this method in their synthesis of ICI-199441.[78]



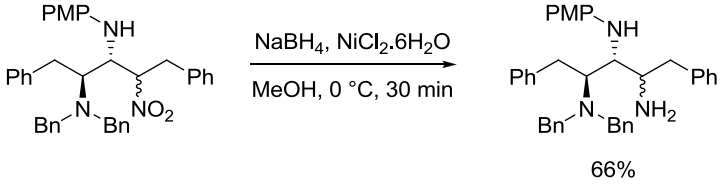
Scheme 52: Raney-nickel reduction and cyclic thiourea formation.

Zinc reductions of *β*-nitroamines have been reported by several different groups. Shibasaki *et al.* used a Zn/NH_4Cl reduction to form the 1,2-diamine required for their synthesis of CP-99994 in high yield.[78] Bernardi and Ricci used a similar protocol but found that the addition of catalytic indium(0) gave drastically improved yields compared to those obtained when using only zinc.[79] Zn/HCl reductions have also been used to great effect. Feng *et al.* reported the use of this method to form 1,2-diamines in excellent yield (Scheme 53).[80] This method was also used by the group of Liu in their synthesis of trifluoromethyl-1,2-diamines.[81]



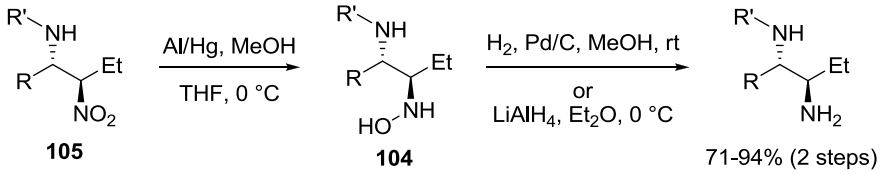
Scheme 53: A Zn/HCl reduction of *β*-nitroamines.

Nickel boride reductions have also been a popular choice for the reduction of *β*-nitroamines, with several groups reporting success when using this reduction protocol. This method has the advantage of having short reaction times and is often high yielding. Bernardi and Ricci demonstrated its use in their synthesis of HIV protease inhibitors (Scheme 54).[82] The groups of Takemoto and Shibasaki have also reported the use of this method.[25b,58a] Johnston *et al.* found the use of cobalt boride to be higher yielding in their recent synthesis of (-)-nutlin-3.[83]



Scheme 54: Nickel boride reduction of *β*-nitroamines.

An alternative mild and efficient reduction protocol using aluminium amalgam was reported by Anderson *et al.* for the reduction of particularly unstable *β*-nitroamines.[84] The reduction initially gives hydroxylamine **104**, which shows much higher stability than that of *β*-nitroamine **105** and can be further reduced using standard hydroxylamine reduction protocols, such as $LiAlH_4$ or hydrogenation over Pd/C. High yields were obtained for the two step process and direct comparison to the SmI_2 reduction method was made showing that the Al/Hg method gave superior results (Scheme 55).



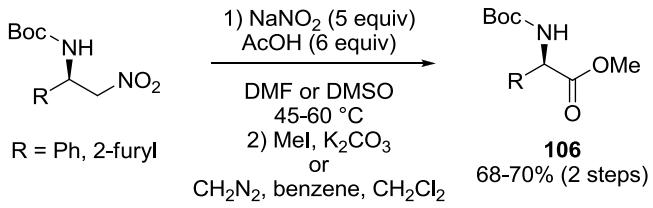
R = Ph, 2-furyl, *n*-pentyl; R' = OMB, PMB, PMP, allyl, $(CH_2)_2OTBS$

Scheme 55: Aluminium amalgam reduction of *β*-nitroamines.

1.4.2 Nef Reaction

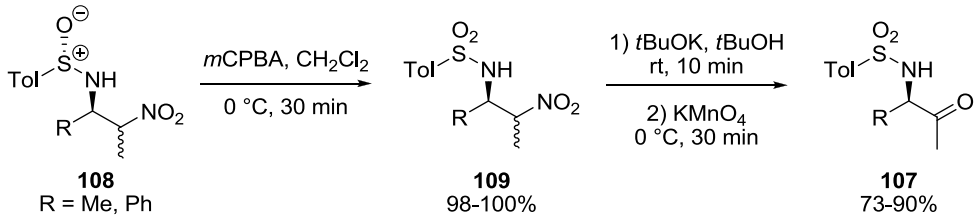
The direct conversion of the nitro group of *β*-nitroamines to a carbonyl group, known as the Nef reaction, is an important transformation allowing for the efficient synthesis of *α*-aminocarbonyl compounds. Several reports detailing this reaction have been given. The

groups of Takemoto, Palomo and Kumaraswamy used standard Nef conditions ($NaNO_2$ and AcOH) for the synthesis of α-aminoacid derivatives **106** in good yields (Scheme 56).[25b,57,85]



Scheme 56: Synthesis of α-aminoacid derivatives *via* the Nef reaction.

Ruano and Cid reported the synthesis of α-aminoketones **107** by an alternative Nef procedure using *t*BuOK and $KMnO_4$ (Scheme 57).[49b] They found that sulfinyl-β-nitroamines **108** were unstable to all Nef conditions attempted, so oxidation to sulfonyl-β-nitroamines **109** was required prior to the Nef reaction. The α-aminoketones **107** could be formed in excellent yield over the two steps.

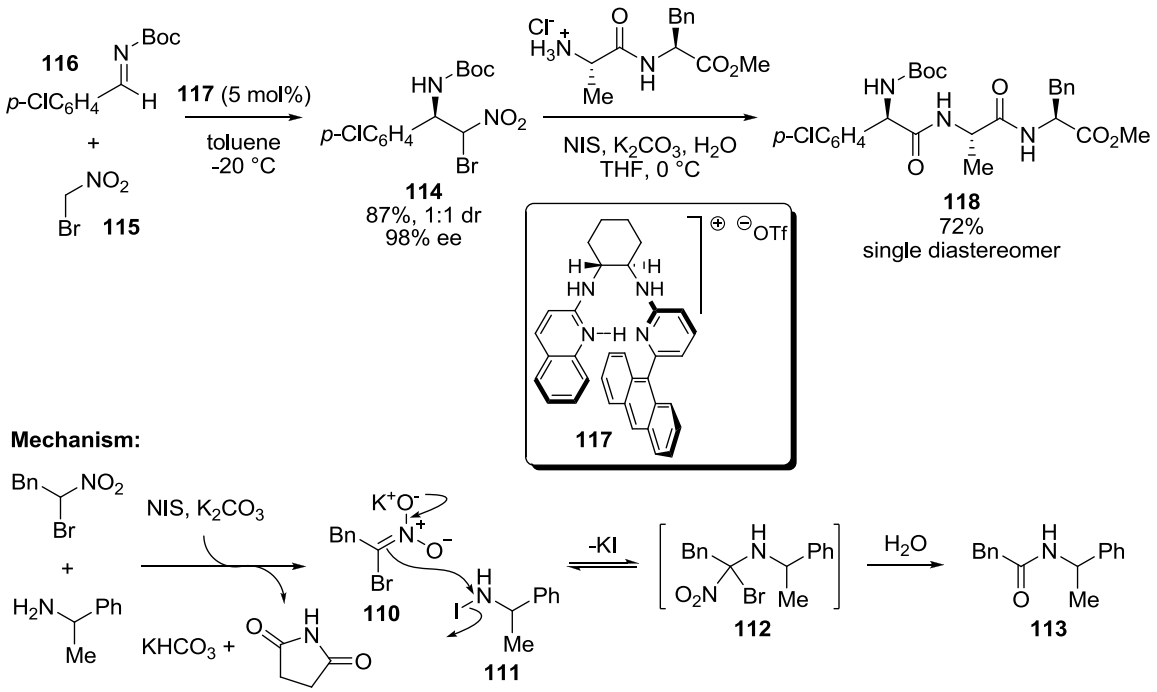


Scheme 57: Synthesis of α-aminoacid derivatives *via* the Nef reaction.

1.4.3 Peptide Synthesis

The group of Johnston published a novel method for the synthesis of amides and peptides that uses the direct coupling of bromonitroalkanes and amines in the presence of an electrophilic iodine source (NIS).[86] The construction of the amide bond results from the nucleophilic attack of the nitronate **110** onto the electrophilic *N*-iodoamine **111**. Hydrolysis of the resulting α-bromo-α-nitroamine **112** gives the amide product **113** (see mechanism in Scheme 58). The bromonitroalkanes function as nucleophilic acyl anion equivalents, demonstrating the first use of umpolung reactivity in amide bond formation. The group went on to demonstrate that β-nitroamine **114**, the product from a nitro-Mannich reaction between bromonitromethane (**115**) and *N*-Boc imine **116** catalysed by chiral proton catalyst **117**, could be subjected to the umpolung chemistry with a range of aminoacid derivatives to

form the corresponding peptides **118** (Scheme 58). Good yields of the peptide products were obtained and no epimerisation of the α-carbonyl positions was observed.



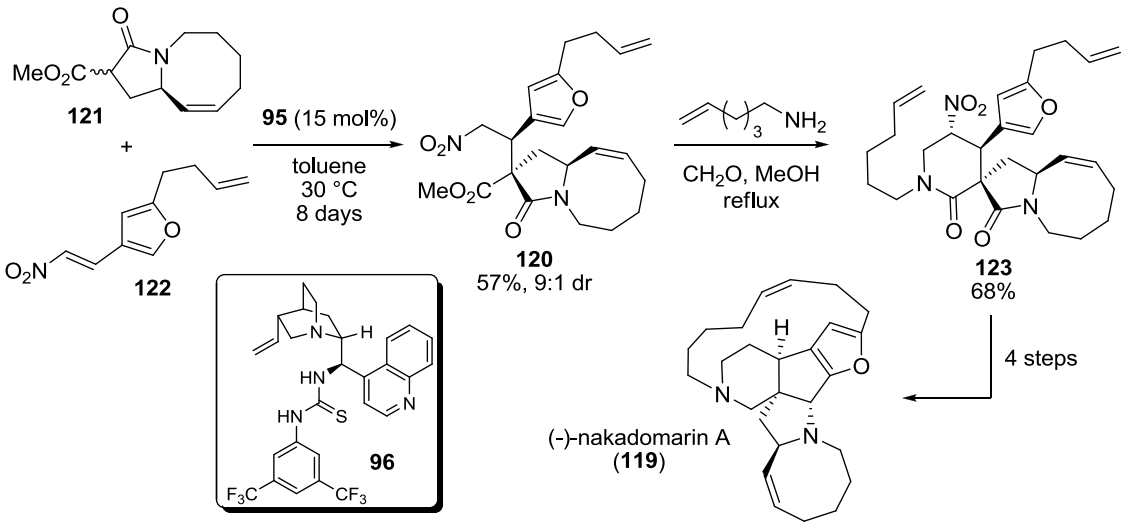
Scheme 58: Umpolung amide bond formation using β-bromo-β-nitroamines.

1.4.4 Application to Synthesis

The efficiency of the nitro-Mannich reaction and the versatility of the β-nitroamine products have unsurprisingly resulted in its application to the synthesis of a number of natural products and pharmaceuticals. These have been performed using a variety of different nitro-Mannich protocols ranging from base mediated diastereoselective reactions to highly enantioselective organocatalytic reactions responsible for creating the key stereogenic centres found in the final product. Some recent examples have been highlighted in the following section.

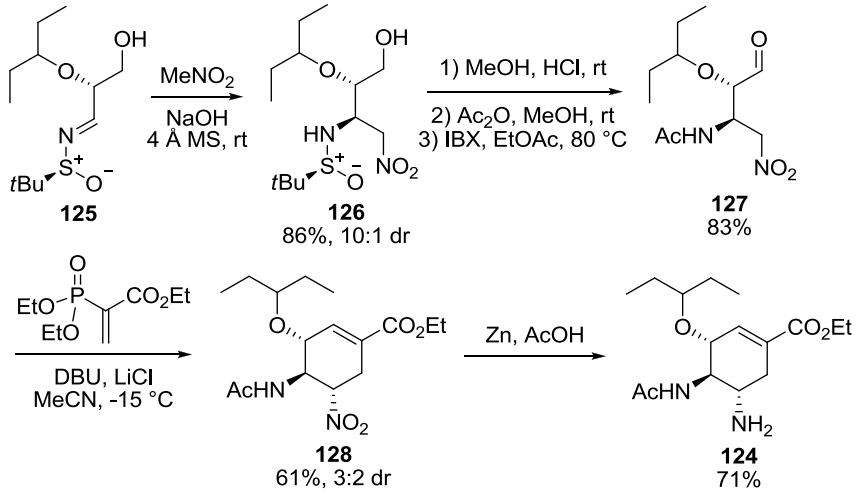
In 2009, Dixon *et al.* used their nitro-Mannich/lactamisation cascade chemistry to synthesise the piperidine core of (-)-nakadomarin A (**119**).[87] They formed γ-nitroester **120** through a diastereoselective Michael addition of malonate **121** to nitroalkene **122**, catalysed by thiourea **96**. Heating **120** in the presence of formaldehyde and hex-5-enamine led to the

formation of 5-nitropiperidin-2-one **123** in good yield. This was subsequently converted to (-)-nakadomarin A (**119**) in four further steps (Scheme 59).



Scheme 59: Synthesis of (-)-nakadomarin A (**119**).

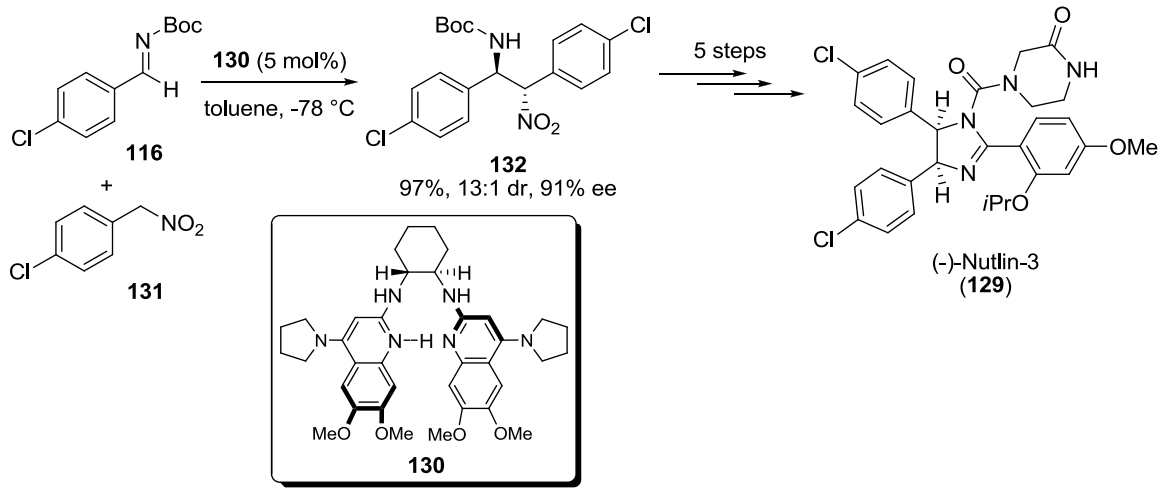
In 2010, the group of Lu demonstrated that the nitro-Mannich reaction could be used for the synthesis of oseltamivir (**124**), the free amine of Tamiflu™ (**8**).[88] They used a highly diastereoselective base mediated nitro-Mannich reaction between nitromethane and *N*-sulfinyl-imine **125** to form *β*-nitroamine **126** (Scheme 60). Four further steps including a Michael/Horner-Wadsworth-Emmons cascade of nitroaldehyde **127** and reduction of the resulting cyclic *β*-nitroamine **128** provided oseltamivir (**124**).



Scheme 60: Synthesis of oseltamivir (**124**).

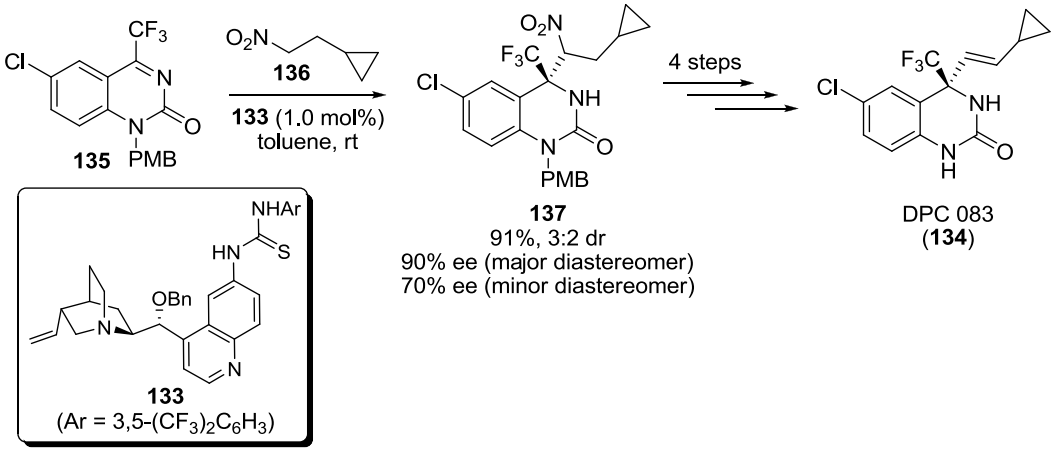
In 2011, Johnston *et al.* published their synthesis of the potent p53/MDM2 inhibitor (-)-Nutlin-3 (**129**), originally discovered by Hoffmann-La Roche.[83] They used chiral bis-

amidine catalyst **130** to catalyse the reaction between *N*-Boc-aryl-imine **116** and aryl nitromethane **131** (Scheme 61). The resulting *β*-nitroamine **132** was formed in exceptional yield and stereoselectivity, providing the desired stereochemistry in 13:1 dr (*anti*) and 91% ee. Reduction of the nitro group followed by a series of amide bond formations and cyclisation to form the imidazoline ring furnished (-)-Nutlin-3 (**129**) in 42% yield over five steps.



Scheme 61: Synthesis of (-)-Nutlin-3 (**129**).

In the same year, W. Wang *et al.* developed thiourea catalyst **133** for the nitro-Mannich reaction of nitroalkanes with cyclic trifluoromethyl ketimines. They then applied their conditions to the synthesis of the anti-HIV drug DPC 083 (**134**).[89] The nitro-Mannich reaction between ketimine **135** and nitroalkane **136** proceeded in excellent yield giving *β*-nitroamine **137** in 91% yield, albeit in poor diastereoselectivity (Scheme 62). Completion of the synthesis of DPC 083 (**134**) was accomplished in a further four steps.



Scheme 62: Synthesis of DPC 083 (**134**).

1.5 The Conjugate Addition Nitro-Mannich Reaction

The conjugate addition nitro-Mannich reaction involves the Michael addition of a nucleophile, be it a hydride, heteroatom or carbon based, to a nitroalkene to form a nitronate species. This nitronate can then be trapped by an electrophile, such as an imine, resulting in a nitro-Mannich reaction (Figure 9). The benefits of this reaction include the rapid formation of up to three contiguous stereocentres and the generation of high levels of molecular complexity from simple starting materials. The use of nitroalkenes is favourable over nitroalkanes as they can be easily prepared from the corresponding aldehyde through a Henry condensation reaction with nitromethane.

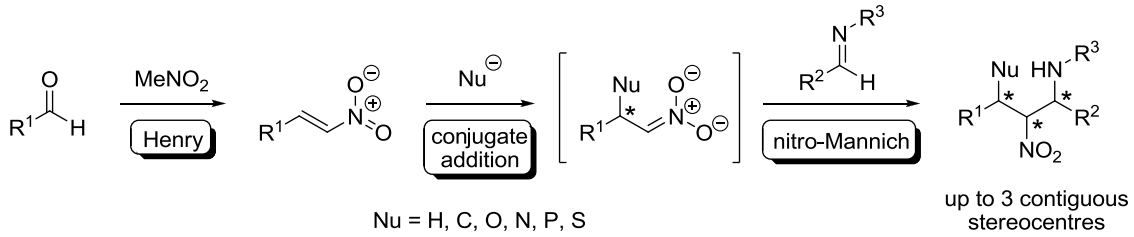


Figure 9: The conjugate addition nitro-Mannich reaction.

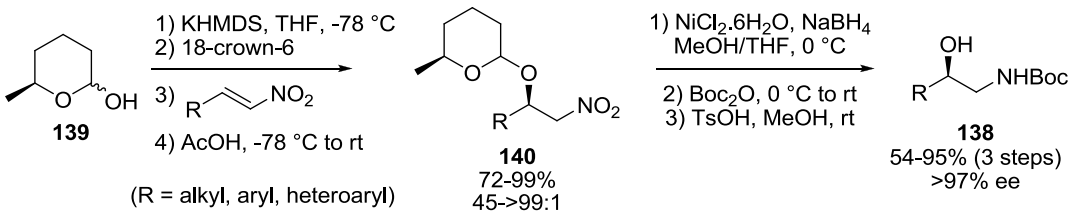
As conjugate addition reactions to nitroalkenes constitute a considerable amount of the work reported in this thesis a brief review of the literature regarding this topic has been given in the following section.

1.5.1 Conjugate Additions to Nitroalkenes

Nitroalkenes are excellent Michael acceptors due to the strong electron-withdrawing character of the nitro group. Conjugate additions to nitroalkenes can, therefore, be performed under relatively mild conditions and are tolerant of various functional groups. Furthermore, the products formed from conjugate additions to nitroalkenes are highly valuable as a result of the versatility of the nitro group. Consequently, numerous studies aimed towards asymmetric conjugate additions have been completed. Various nucleophiles have been employed in these reactions including oxygen, sulfur, nitrogen (see section 1.2.3 for some examples), phosphorus and carbon.[76]

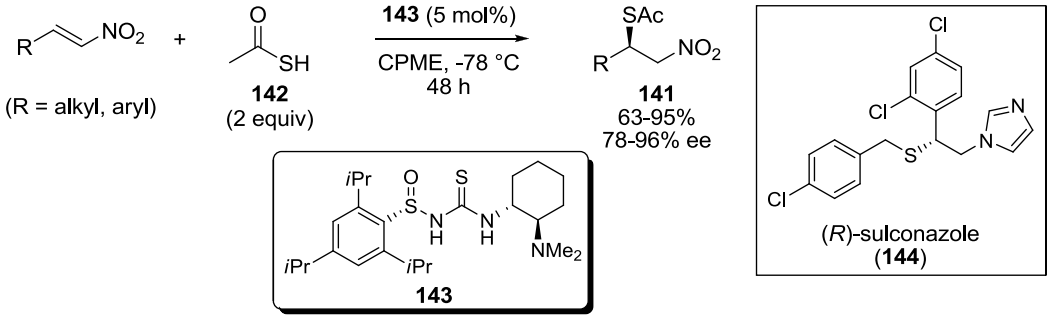
1.5.1a Heteroatom Nucleophiles

Dixon *et al.* described the asymmetric synthesis of 1,2-amino alcohols **138** by an oxy-Michael addition of the anion of enantiopure *δ*-lactol **139** to nitroalkenes.[90] The reactions proceeded in excellent yield and diastereoselectivity and the products **140** could be easily converted into the corresponding 1,2-amino alcohols by nitro reduction and removal of the tetrahydropyran auxiliary (Scheme 63).



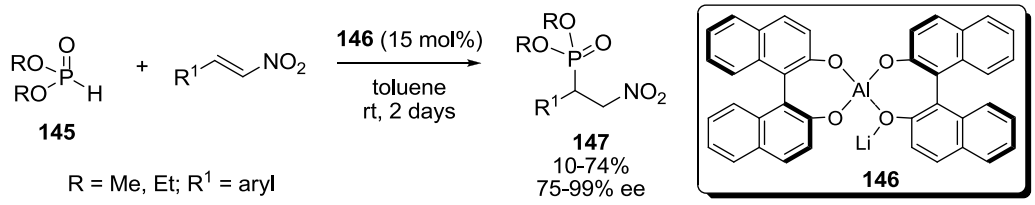
Scheme 63: Diastereoselective oxy-Michael reaction.

Ellman *et al.* described their synthesis of *β*-nitrothioacetates **141** by the organocatalysed conjugate addition of thioacetic acid (**142**) to nitroalkenes.[91] They used chiral sulfinyl thiourea catalyst **143** for the addition of thioacetic acid to a variety of nitroalkenes in high yield and enantioselectivity (Scheme 64). Furthermore, they demonstrated the utility of this reaction through the first asymmetric synthesis of the antifungal drug (*R*)-sulconazide (**144**).



Scheme 64: Enantioselective addition of thioacetic acid (**142**) to nitroalkenes.

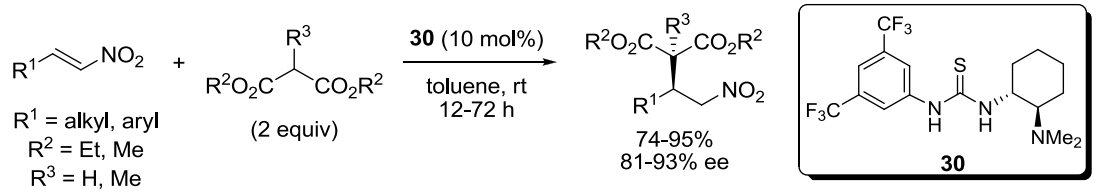
The asymmetric conjugate addition of phosphorus nucleophiles has also been reported. Namboothiri *et al.* reported the conjugate addition of dialkyl phosphites **145** to aryl nitroalkenes catalysed by the Al/Li/bis(binaphthoxide) complex **146** (Scheme 65).[92] The reactions furnished *β*-nitrophosphonates **147** in moderate to good yield and with excellent enantioselectivity.



Scheme 65: Enantioselective addition of dialkyl phosphites (**145**) to nitroalkenes.

1.5.1b Carbon Nucleophiles

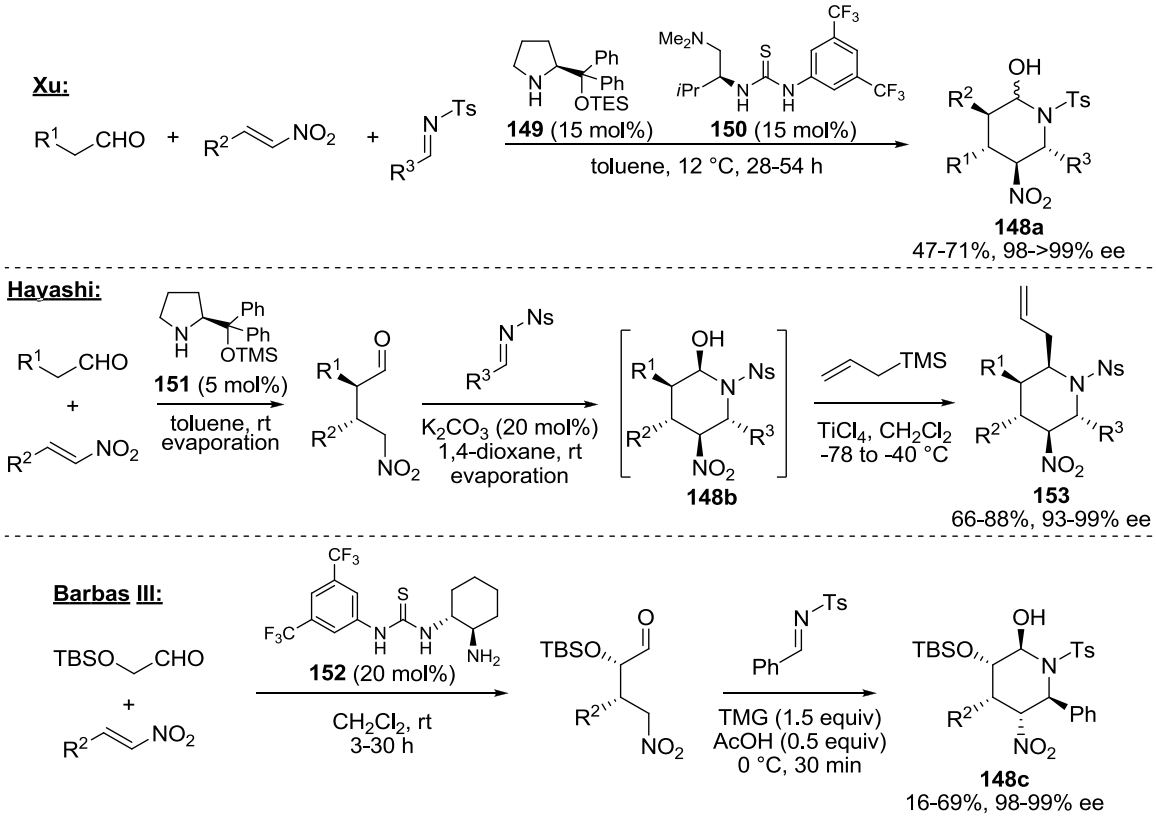
The conjugate addition of carbon-based nucleophiles has also been studied extensively. These often involve activated nucleophiles such as malonates and other carbonyl compounds. The chiral thiourea catalysed conjugate addition of malonates to nitroalkenes by Dixon *et al.* was mentioned briefly in section 1.3.6 (Scheme 49).[73] The group of Takemoto also reported an enantioselective conjugate addition of malonates to nitroalkenes catalysed by their chiral thiourea catalyst **30** (Scheme 66).[24]



Scheme 66: Enantioselective addition of malonates to nitroalkenes.

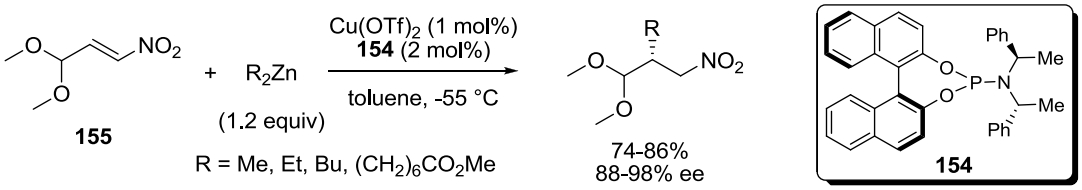
Although organocatalysis provides a very attractive method for achieving asymmetric conjugate additions, the trapping of the resulting nitronate is difficult due to competing protonation by the cationic catalyst species. To date, methods reported for conjugate addition nitro-Mannich reactions have generally proceeded *via* protonation of the nitronate species. Addition of a base or heating was then required to reform the nitronate and promote the desired nitro-Mannich reaction (an exception to this is the aza-Morita-Baylis-Hillman reaction reported by Xu *et al.*[71] in section 1.3.6). Examples of conjugate addition nitro-Mannich reactions of this type include the conjugate addition/nitro-Mannich/lactamisation reactions by Dixon *et al.*[73] (see Scheme 49, section 1.3.6) and three reports by the groups of Xu, Hayashi and Barbas III.[93,94,95] These groups used similar chemistry for the synthesis of hemiaminals **148**, *via* the asymmetric organocatalysed conjugate addition of aldehydes to nitroalkenes and subsequent reaction of the resulting

nitroalkane with an imine in a nitro-Mannich/hemiaminalisation reaction sequence (Scheme 67). Xu *et al.* utilised two organocatalysts, prolinol **149** to catalyse the conjugate addition and thiourea **150** to catalyse the nitro-Mannich/hemiaminalisation, in a one-pot three-component cascade reaction sequence. Hemiaminals **148a** were formed with excellent stereoselectivity but only moderate yield.[93] Hayashi *et al.* used the similar prolinol **151** to catalyse the conjugate addition reaction. In order to affect the desired nitro-Mannich/hemiaminalisation reaction a solvent swap to 1,4-dioxane and the introduction of an *N*-nosyl-imine and catalytic K_2CO_3 was required. The group also demonstrated that the hemiaminals **148b** could be substituted with allyltrimethylsilane, furnishing piperidine **153** in good yield and excellent enantio- and diastereoselectivity.[94] The drawback of this method is that it requires two solvent swaps to achieve good yields and selectivities. Barbas III *et al.* used thiourea catalyst **152** to promote the conjugate addition reaction. Although no solvent swaps were required, the addition of *N*,*N*,*N*',*N*'-tetramethylguanidine (TMG) and acetic acid was required to achieve good yields and stereoselectivities of hemiaminals **148c**.[95] The group also failed to demonstrate such a broad substrate scope as that demonstrated by Xu and Hayashi.



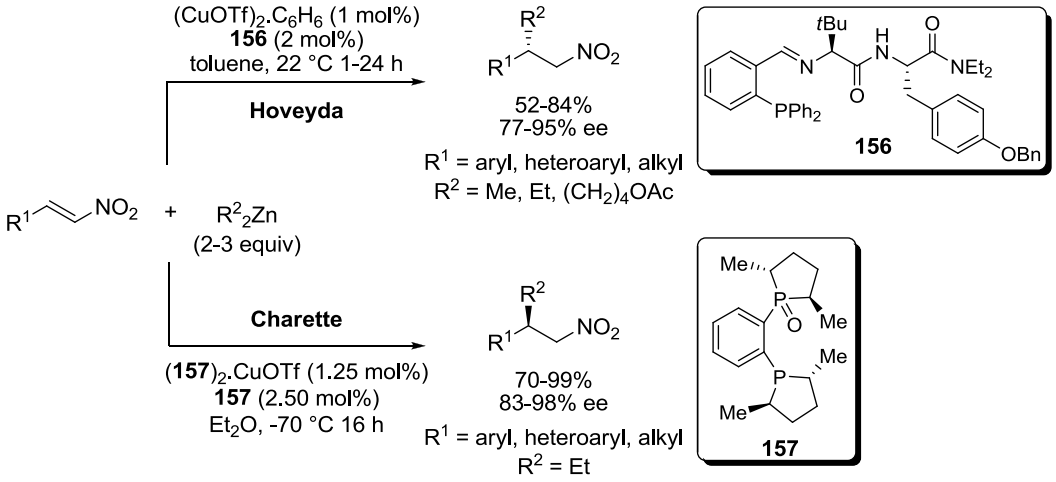
Scheme 67: Conjugate addition nitro-Mannich reactions.

The use of organometallic reagents in conjugate additions to nitroalkenes is also well documented in the literature. This potentially provides an advantage over organocatalytic methods as the resulting metal-nitronate species formed in the reaction will not be protonated until a proton source is added to the reaction. The metal-nitronate could then be trapped using a variety of electrophiles, including imines. Particularly attractive organometallic reagents are diorganozincs, for which there are a number of highly enantioselective protocols available. Feringa *et al.* reported the use of phosphoramidite ligand **154** in highly enantioselective Cu(II)-catalysed conjugate additions of a number of dialkylzinc reagents to nitroalkene **155** (Scheme 68).[96]



Scheme 68: Asymmetric conjugate addition of dialkylzincs to nitroalkene **155**.

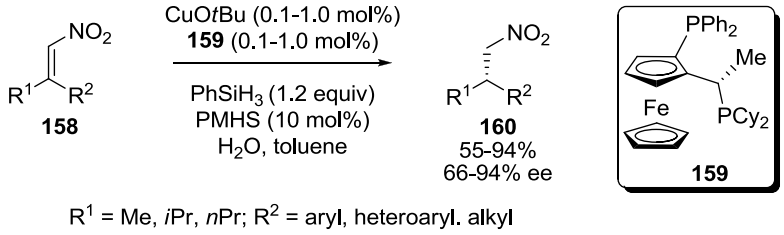
Hoveyda *et al.* extended this methodology to a wide range of aryl and alkyl nitroalkenes.[97] They used the chiral dipeptide phosphine ligand **156** in Cu-catalysed conjugate additions of a number of dialkylzinc reagents, achieving high yields and enantioselectivities (Scheme 66).[97a] This methodology was later extended to trisubstituted nitroalkenes.[97b] The group of Charette published a similar protocol that used chiral bis(phosphine) monoxide ligand **157** for the addition of diethylzinc to nitroalkenes (Scheme 69).[98] A range of other procedures utilising alternative catalysts have also been reported.[99]



Scheme 69: Asymmetric conjugate addition of dialkylzincs to nitroalkenes.

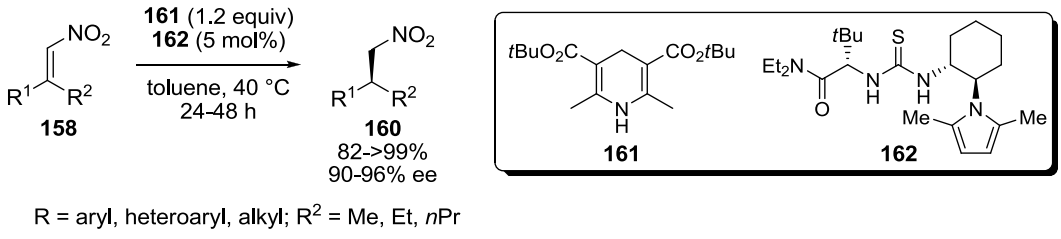
1.5.1c Hydride Nucleophiles

The conjugate addition of hydride nucleophiles to nitroalkenes is well documented in the literature, especially the use of borohydride reductants, as it is one of the most straightforward methods for producing complex nitroalkanes.[76,100] Several asymmetric methodologies have also been developed that utilise alternative hydride sources. Carreira *et al.* used an *in situ* generated copper hydride, formed from copper(I) *tert*-butoxide and a combination of phenylsilane and polymethylhydrosiloxane (PMHS), to reduce a variety of *β*,*β*-disubstituted nitroalkenes **158** (Scheme 70).[101] The use of (*S*,*R*)-Josiphos (**159**) as a chiral ligand allowed the formation of nitroalkanes **160** in excellent yields and enantioselectivities.



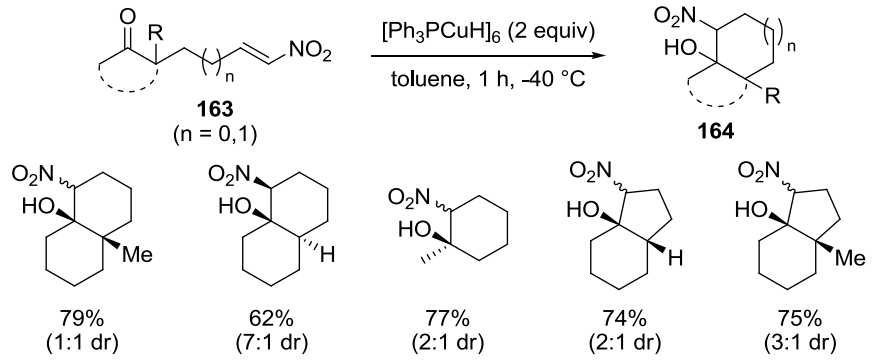
Scheme 70: Asymmetric hydride reduction of nitroalkenes.

An alternative method for the reduction of nitroalkenes is the use of transfer hydrogenations. List *et al.* reported a highly enantioselective organocatalytic transfer hydrogenation of nitroalkenes.[102] The use of dihydropyridine **161** and thiourea **162** promoted the reduction of a variety of *β*,*β*-disubstituted nitroalkenes **158** in excellent yields and enantioselectivities (Scheme 71). Carreira *et al.* later reported a highly enantioselective iridium diamine complex-catalysed transfer hydrogenation of similar trisubstituted nitroalkenes that utilised formic acid as the hydrogen source.[103]



Scheme 71: Asymmetric transfer hydrogenation of nitroalkenes.

Although the reduction of nitroalkenes is well documented, the subsequent trapping of the nitronate intermediate formed in the conjugate addition reaction has received very little attention. There has, to our knowledge, been only a single example of a conjugate addition nitro-Mannich reaction that utilises a hydride nucleophile (a reductive nitro-Mannich reaction). This was reported by Walser *et al.* in 1978 and is depicted in Scheme 26 (Section 1.3.1).[47] The $NaBH_4$ reduction of the exocyclic nitroalkene in **60** resulted in a transannular nitro-Mannich reaction to form the bridged cyclic *β*-nitroamine **61**. There has also been an example of a reductive Henry reaction. This was reported by Chiu *et al.* who used Stryker's reagent ($[Ph_3PCuH]_6$) to perform a hydride conjugate addition to nitroalkenes **163** bearing a tethered ketone moiety (Scheme 72).[104] The copper-nitronate species formed subsequently reacted with the tethered ketone in an intramolecular Henry reaction. The bicyclic *β*-nitroalcohol products **164** were formed in good yield but with poor diastereoselectivity.

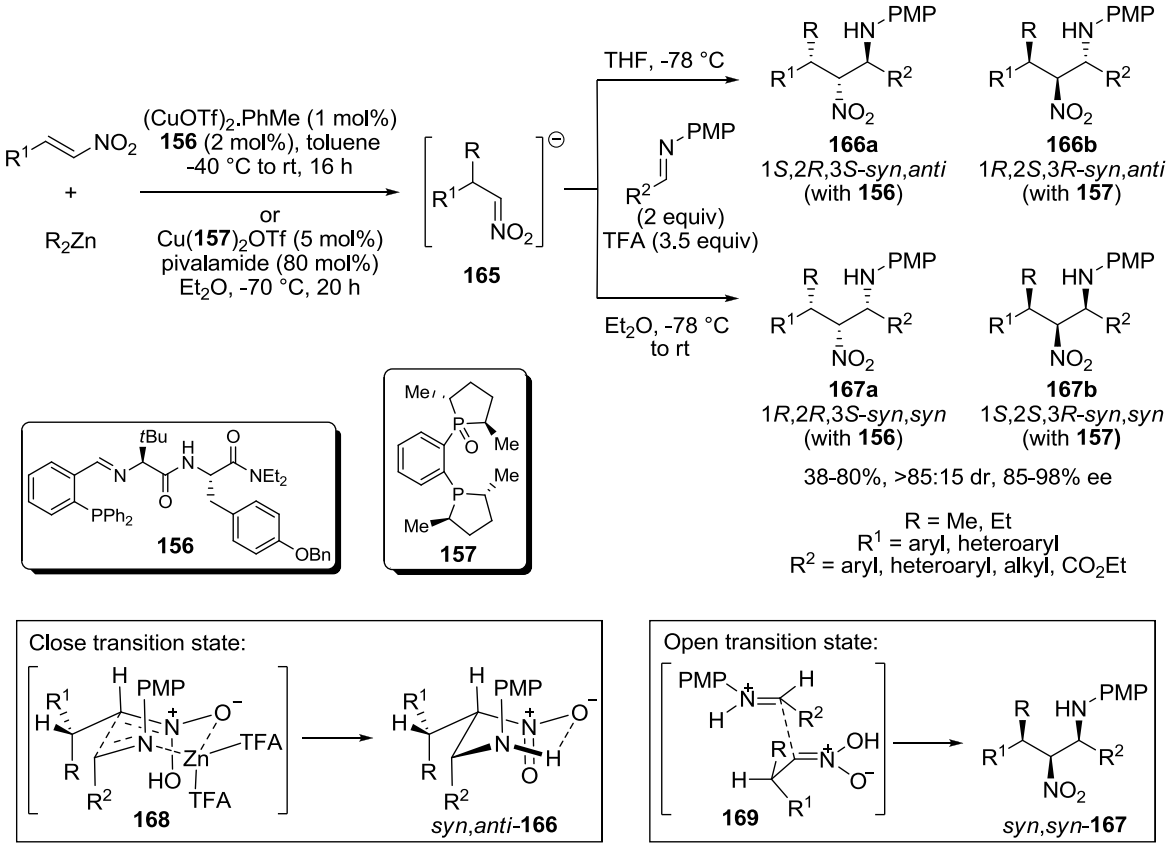


Scheme 72: A reductive intramolecular Henry reaction.

1.5.2 Acyclic *β*-Nitroamines *via* Conjugate Addition Nitro-Mannich Reactions

Inspired by the works of Feringa, Hoveyda and Charette,[96,97,98] Anderson *et al.* investigated the application of dialkylzinc conjugate addition protocols to conjugate addition nitro-Mannich reactions.[105] The group were able to perform highly diastereoselective nitro-Mannich reactions by the introduction of *N*-PMP-imines to the *in situ* generated zinc-nitronates **165**. Selective formation of either the *anti-β*-nitroamines **166a** and **166b** or the rare *syn-β*-nitroamines **167a** and **167b** with excellent stereocontrol over three contiguous stereocentres was achieved by variation of the solvent used in the nitro-Mannich reaction and the ligand used in the conjugate addition reaction (Scheme 73). The procedure gave uniformly high yields and stereoselectivities for a range of aryl/heteroaryl nitroalkenes

and aryl/heteroaryl/alkyl imines. They explain that the observed diastereoselectivity arises from the differing solubility of $Zn(O_2CCF_3)_2$, formed upon addition of TFA to the reaction mixture, in THF and Et_2O. When the reactions were performed in THF the $Zn(O_2CCF_3)_2$ remained in solution. Coordination of the nitronate and imine to the Zn^{2+} species enables the formation of closed chair-like transition state **168** and, with the chiral nitronate side chain occupying an equatorial orientation, leads to the *syn*,*anti*-diastereomers **166a** and **166b**. The poor solubility of $Zn(O_2CCF_3)_2$ in Et_2O resulted in precipitation of this species from the reaction. With no Zn^{2+} species available to form a coordinated complex, the reaction proceeds *via* open transition state **169**, leading to the *syn*,*syn*-diastereomers **167a** and **167b**. This procedure represents a highly versatile method for the synthesis of *β*-nitroamines as it provides access to the products in a number of enantiomeric and diastereomeric configurations in a highly stereocontrolled fashion.

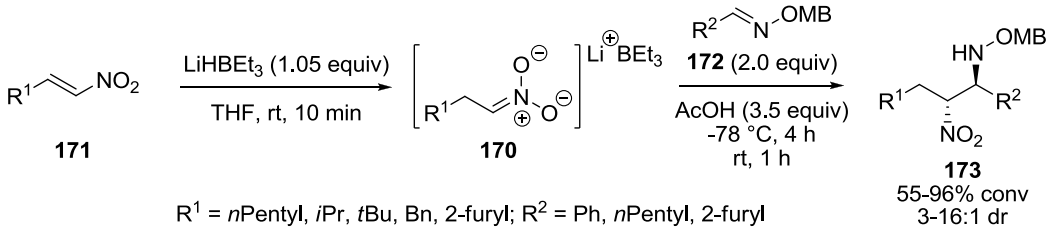


Scheme 73: Asymmetric dialkylzinc conjugate addition nitro-Mannich reactions.

This reaction and the aza-Morita-Baylis-Hillman reaction reported by Xu *et al.*[71] (see Scheme 47 in section 1.3.6) represent the only examples of conjugate addition nitro-Mannich reactions that involve direct trapping of the nitronate formed in the

conjugate addition. Unlike other reported procedures, they do not proceed *via* a nitroalkane (or nitronic acid) intermediate, therefore, eliminating the need to reform the nitronate species with additional reagents or heating, which may not tolerate certain sensitive functional groups. Furthermore, they allow the formation of less stable acyclic *β*-nitroamines, which is in contrast to other conjugate addition nitro-Mannich reactions which have only been successfully applied to the formation of cyclic products such as piperidinones and piperidines (see Schemes 26 and 66).

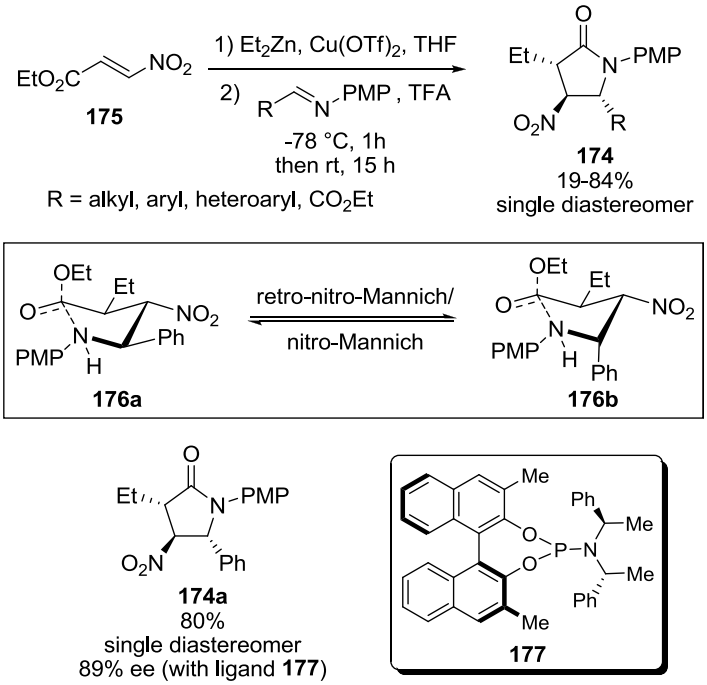
The Anderson group have expanded the scope of their conjugate addition nitro-Mannich methodology to include the use of hydride nucleophiles and also to the formation of pyrrolidinones.[106,107] The use of $LiHBEt_3$ (Superhydride™) in conjugate additions to nitroalkenes, originally reported by Kabalka *et al.*,[100] provides the relatively stable lithium borane nitronate species **170** which can subsequently be trapped by the addition of an imine and a Brønsted acid. Anderson *et al*. showed that this reductive nitro-Mannich procedure was applicable to a range of nitroalkenes **171** and alkyl/aromatic *N*-OMB-imines **172**, giving *β*-nitroamines **173** in excellent conversion and good *anti* diastereoselectivities (Scheme 74).[106] The reaction, however, appeared to be limited to the use of alkyl nitroalkenes as when aromatic nitroalkenes were employed poor conversion and/or diastereoselectivity was observed.



Scheme 74: A reductive nitro-Mannich reaction.

The same group also applied their dialkylzinc conjugate addition nitro-Mannich reaction protocol to the synthesis of pyrrolidinones **174** (Scheme 75).[107] A conjugate addition nitro-Mannich/lactamisation reaction was achieved by using nitroacrylate **175**. The reaction was performed with a wide range of *N*-PMP-imines to form pyrrolidinones **174** in moderate to good yields and excellent diastereoselectivity. The observation of only a single diastereomer of pyrrolidinone **174** was explained by the selective lactamisation of *syn,anti-β*-nitroamine **176a**, which can adopt a conformation with all substitutents in *pseudo*-equatorial positions, over *syn,syn-β*-nitroamine **176b**. A retro-nitro-Mannich/nitro-

Mannich sequence gradually converts the remaining *syn*,*syn*-*β*-nitroamine **176b** into the *syn*,*anti*-*β*-nitroamine **176a**, which can subsequently undergo lactamisation. The development of an asymmetric variant was accomplished through the use of phosphoramidite ligand **177** in the $Cu(OTf)_2$-catalysed conjugate addition of diethylzinc to nitroacrylate **175**, originally reported by Sewald *et al.*[108] The subsequent nitro-Mannich/lactamisation sequence enabled the formation of pyrrolidinone **174a** in excellent yield and enantioselectivity. This method represents a one-pot alternative to the nitro-Mannich/lactamisation methodology reported by Dixon *et al.*, which requires sequential alkylation and nitro-Mannich/lactamisation steps (see Scheme 50).[75]



Scheme 75: A conjugate addition nitro-Mannich/lactamisation reaction.

1.6 1,2-Diamines in Fused Heterocycles

Many fused nitrogen heterocycles are considered to be privileged structures. That is, they are capable of binding selectively to a range of different biological targets through judicious modification of their structures.[109] The result is that these molecules demonstrate a variety of biological activities and have, consequently, been the functional group of choice in many campaigns aimed towards the development of new pharmaceuticals. Incorporation of a 1,2-diamine motif, also a privileged structure, generates a class of compounds that possess two important functional groups and could have important applications in both medicinal and synthetic chemistry. Indolines and tetrahydroquinolines are two of the many fused hetereocycles that fall into the privileged structure category and they are both present in a variety of natural products and medicinal agents displaying a range of interesting biological activitites.[110,111] Incorporation of a 1,2-diamine into these structures could generate 2-aminomethylene indoline and 3-aminotetrahydroquinoline scaffolds. The research presented in this thesis has focused on the synthesis of these two types of 1,2-diamine containing fused heterocycles. These structures are also present in a number of interesting natural products and pharmacological agents. The following section will briefly highlight the importance of these structures in biological systems and present some of the current methods available for their preparation.

1.6.1 Biological Importance

The 2-aminomethylene indoline scaffold is present in a large number of natural products. It is, however, less common than the 2-aminomethylene indole scaffold, which is a biosynthetic intermediate of 2-aminomethylene indoline formation. However, like the 2-aminomethylene indole derivatives, of which there are a large number of natural products and pharmacological agents, the 2-aminomethylene indolines also display a range of interesting biological activities. Ajmaline (**178**) is a 2-aminomethylene indoline alkaloid isolated from *Rauwolfia serpentine*. It displays strong antiarrhythmic effects and is used in the therapy of cardiovascular diseases (Figure 10).[112] Schizozygine (**179**), an anti-fungal agent, was isolated from the *Schizozygia caffaeoides* (Boj.) Baill., an east African plant which has been used in traditional medicine in Kenya for the treatment of skin diseases.[113] The bis-indole alkaloids alstomacroline (**180**), villalstonine (**181**) and villastonine (**182**),

isolated from various species of *Alstonia* trees in southeast Asia, all exhibit high anti-malarial activities.[114] A variety of other structurally related 2-aminomethylene indoline alkaloids have also been isolated from different *Alstonia* species and have possible applications in the treatment of cancer, malaria, diabetes and high blood pressure.[115]

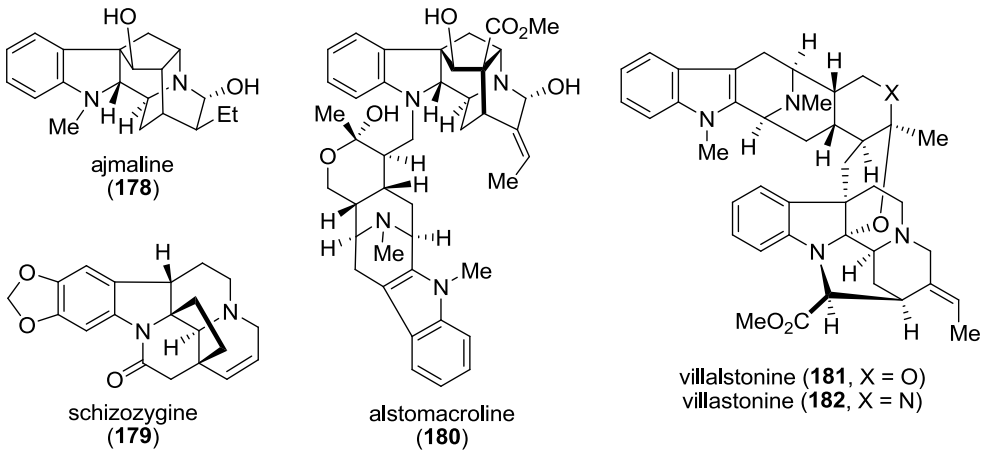


Figure 10: Natural products containing 2-aminomethylene indolines.

The application of the 2-aminomethylene indoline scaffold to medicinal chemistry has been widely studied (Figure 11). Saxena *et al.* developed the potent anti-psychotic agent **183**, which showed improved D_1, D_2 and 5-HT_{2C} receptor blocking activity compared to risperidone, a drug currently used to treat schizophrenia, bipolar disorder and autism (Figure 11).[116] The pyridine derived 2-aminomethylene indoline **184** is a highly selective full 5-HT_{2C} receptor agonist developed by Hoffman-La Roche. It acts as an appetite suppressant for the treatment of obesity.[117] Mitkin *et al.* investigated the effectiveness of pyrroloindolines as 5-HT_6 receptor antagonists, which could be applied to the treatment of cognitive disorders, and found sulfonamide derivative **185** to give good activity.[118] Takayama *et al.* investigated the effect of masking the reactivity of the indole nuclei at the β-position of mitragynine derivatives on their analgesic activities. Treatment of the indole alkaloids with hypervalent iodine in the presence of ethylene glycol provided 2,3-ethylene glycol bridged adducts. These showed improved bioactivity and led to the identification of the fluorinated analogue **186** as a potent μ- and κ-opioid receptor agonist.[119]

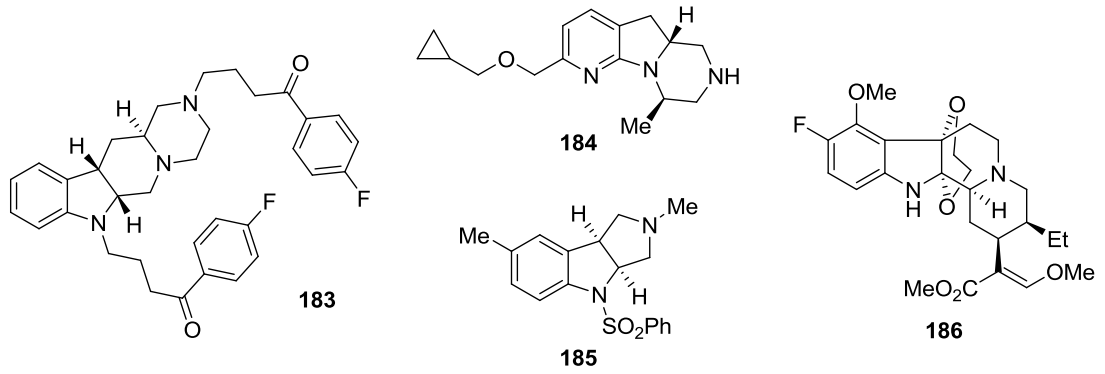


Figure 11: Pharmacological agents containing a 2-aminomethylene indoline.

The 3-aminotetrahydroquinoline scaffold is far less commonly found in nature than the 2-aminomethylene indoline. The isolation of only two types of natural product containing this structural motif have been reported. These include strychnochromine (**187**), an unusual pentacyclic alkaloid containing an unprecedented 2,2,4,4-tetrasubstituted-3-aminotetrahydroquinoline. It was originally isolated from the root bark of *strychnos gossweileri* by Quetin-Leclercq *et al.* in 1988 and the structure was revised in 1991 (Figure 12).[120] The anachelins (anachelin H (**188**), anachelin-1 (**189**) and anachelin-2 (**190**)) are a series of structural isomers isolated from the freshwater cyanobacteria *Anachena cylindrical*. They are comprised of an interesting blend of polyketide, peptide and alkaloid fragments, the latter being a substituted 3-aminotetrahydroquinoline, and are postulated to serve as bacterial growth factors facilitating iron uptake (so-called siderophores).[121]

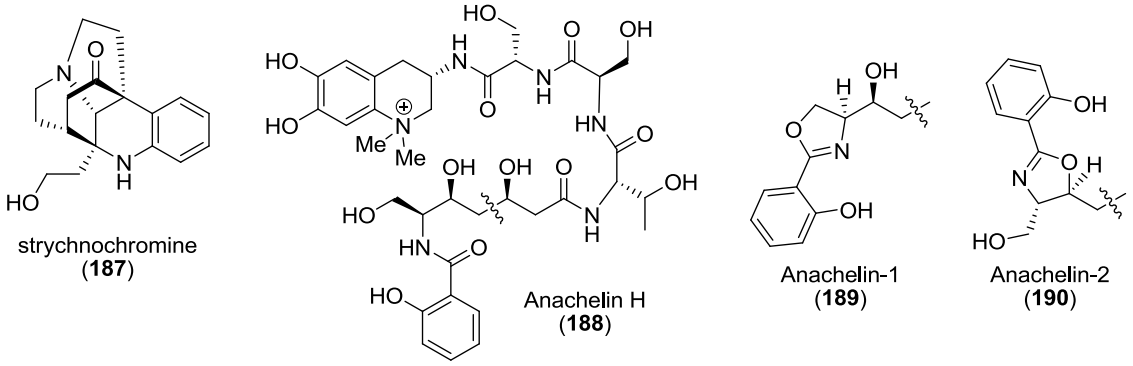


Figure 12: Natural products containing a 3-aminotetrahydroquinoline.

Although uncommon in natural products, the 3-aminotetrahydroquinoline scaffold has been successfully applied to medicinal chemistry. Sumanirole maleate (PNU-95666E, **191**) is a selective and high affinity agonist at the dopamine D_2 receptor developed for the treatment of Parkinson's disease (Figure 13).[122] Similar structures have also been studied including

(*S*)-903 (**192**), which was identified as a positive inotropic agent,[123] and imidazole containing structures **193**, which are inhibitors of farnesyltransferase (FT) and display both anti-tumour and anti-malarial activities.[124]

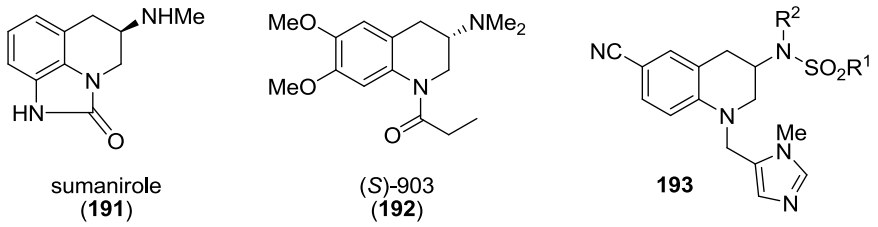
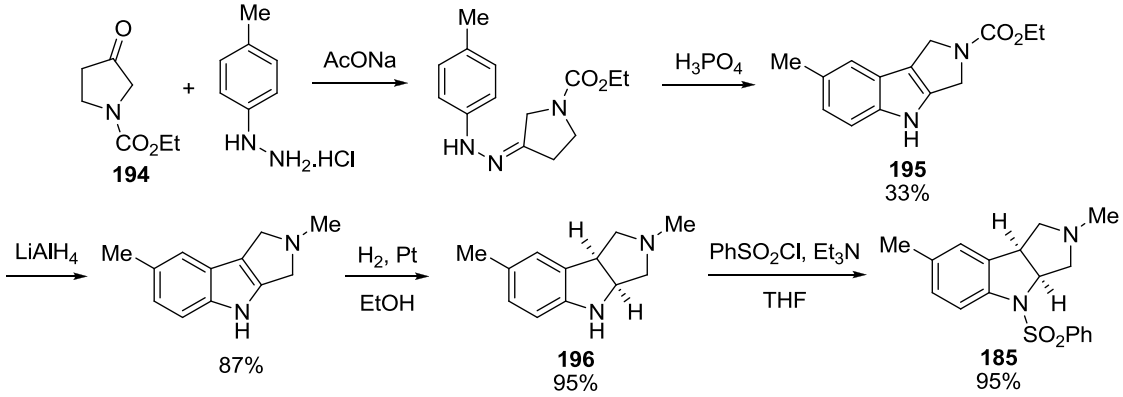


Figure 13: Pharmacological agents containing a 3-aminotetrahydroquinoline.

1.6.2 Synthesis

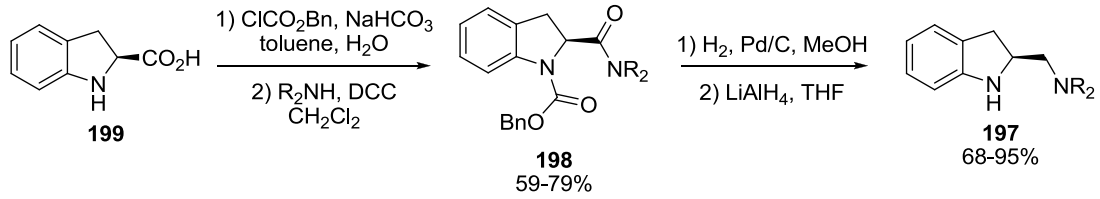
The synthesis of tetrahydroquinolines and indolines has been well documented in the literature.[110,111] The broad range of methods available will, however, not be detailed in this thesis as the following section will focus on the current methods used for the synthesis of 2-aminomethylene indolines and 3-aminotetrahydroquinolines.

The majority of 2-aminomethylene indoline syntheses reported proceed *via* reduction of the corresponding 2-aminomethylene indole, a scaffold that can be easily prepared using a variety of methods, such as the Pictet-Spengler reaction of tryptamine derivatives.[125] An example of the synthesis of 2-aminomethylene indolines from the corresponding indoline was reported by Mitkin *et al.* who utilised a Fischer indole synthesis approach to synthesise the 5-HT_6 receptor antagonist **185** (Scheme 76).[118] Performing the Fischer indole synthesis with pyrrolidin-3-one **194** provided 2-aminomethylene indole **195** which could be converted to the 2-aminomethylene indoline **196** by hydrogenation over a platinum catalyst.



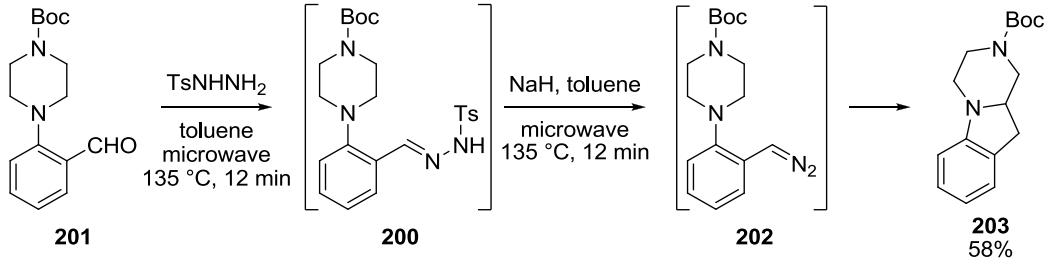
Scheme 76: Fisher indole synthesis route to 2-aminomethylene indolines.

Another common approach is to use readily available indoline-2-carboxylic acid derivatives. Asami *et al.* demonstrated this approach in the synthesis of a variety of 2-aminomethylene indoline ligands **197** for use in asymmetric additions of dialkylzincs to aldehydes.[126] They formed amides **198** from commercially available (*S*)-indoline-2-carboxylic acid (**199**). Simple hydrogenolysis of the carbamoyl protecting group followed by reduction of the amide with $LiAlH_4$ provided the desired ligands **197** in good yield (Scheme 77).



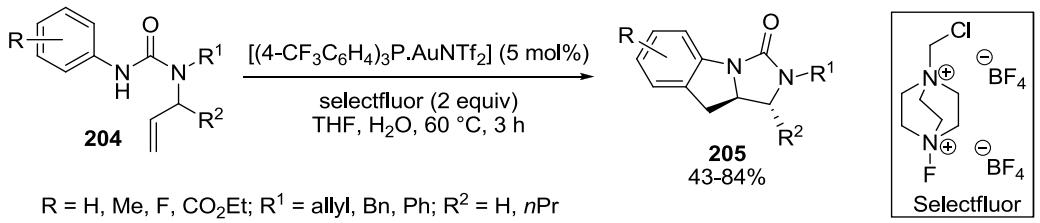
Scheme 77: Amide reduction route to 2-aminomethylene indolines.

An alternative approach that does not rely on reduction of either indole or amide derivatives is the carbene-mediated intramolecular C-H insertion developed by Kehler *et al.*[127] They generated carbenes from phenylpiperazine-derived tosylhydrazones **200**, formed from the corresponding benzaldehyde **201**. Deprotonation with NaH followed by thermal elimination of sulfinate yields the diazo compound **202**. Loss of N_2 generates a carbene which selectively inserts into the C-H bond to form 2-aminomethylene indoline derivative **203** (Scheme 78).



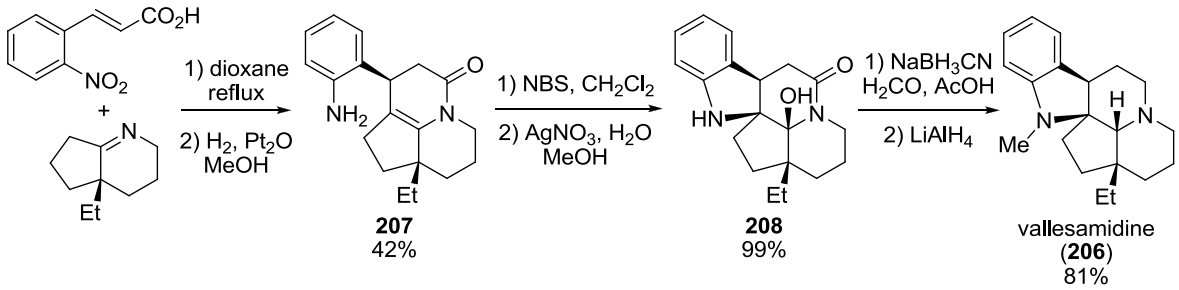
Scheme 78: Intramolecular C-H insertion route to 2-aminomethylene indolines.

Another recent example is the gold-catalysed intramolecular [3+2] annulation approach to tricyclic indolines reported by Zhang *et al.*[128] The reaction of urea **204** with a gold catalyst, in the presence of selectfluor as an oxidant, promoted the oxidative cross coupling reaction between an aryl C-H and an *in situ* generated alkyl gold complex, formed by aminoauration of the allyl group, to form the cyclic urea products **205** in good yields (Scheme 79).



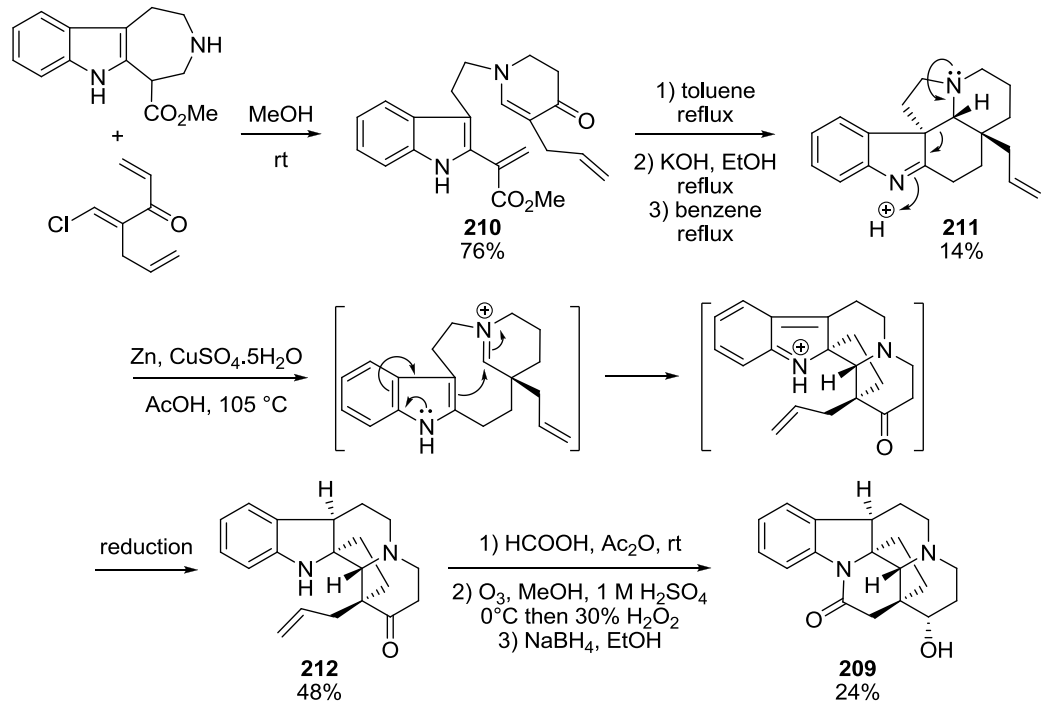
Scheme 79: Gold-catalysed synthesis of 2-aminomethylene indolines.

Various methods have also been used for the synthesis of 2-aminomethylene indoline-containing natural products. These include the synthesis of vallesamidine (**206**) by the group of Heathcock.[129] They synthesised the 2-aminomethylene indoline core *via* an intramolecular bromoamination of enamide **207** to give aminal **208** in excellent yield. Completion of the synthesis of vallesamidine (**206**) was easily achieved by two successive hydride reductions (Scheme 80).



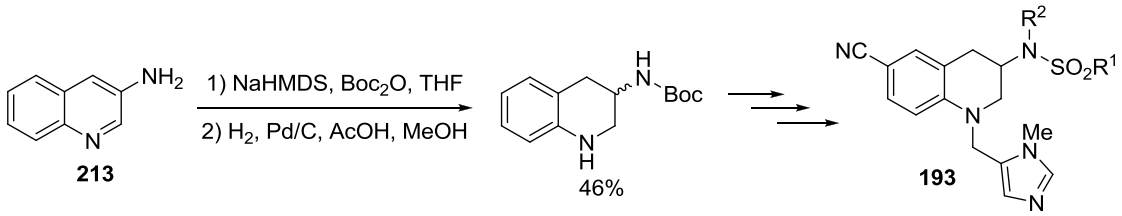
Scheme 80: Synthesis of vallesamidine (**206**).

An alternative approach to a similar 2-aminomethylene indoline-containing natural product was provided by Hájíček *et al.* in their synthesis of 15*α*-hydroxystrempeliopine (**209**) (Scheme 81).[130] They utilised an intramolecular Diels-Alder reaction of indole **210**, which after decarboxylation provided indolenine **211**. This then underwent a zinc-mediated reductive rearrangement to give 2-aminomethylene indoline **212** in moderate yield.



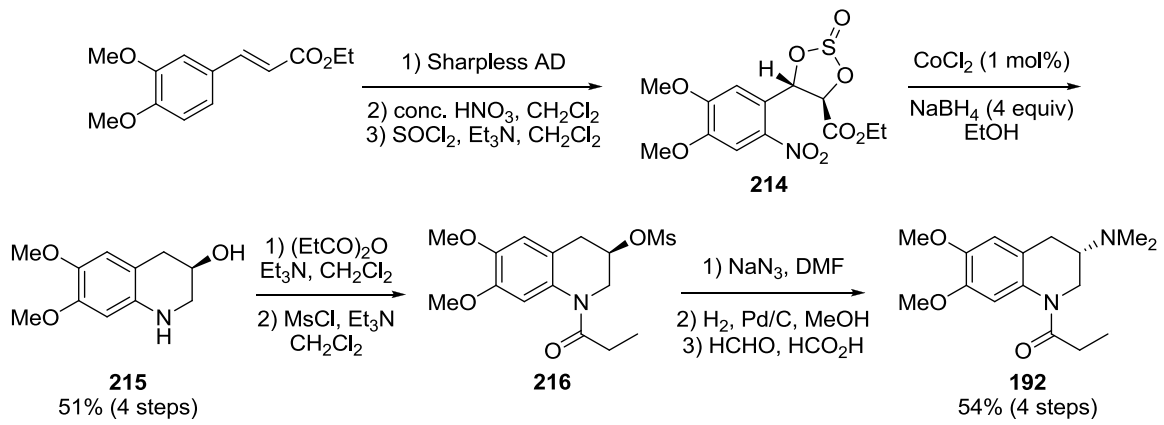
Scheme 81: Synthesis of 15α-hydroxystrempeliopine (**209**).

A number of different methods have been used for the synthesis of the 3-aminotetrahydroquinoline structures shown in Figures 12 and 13. Lombardo *et al.* used the hydrogenation of 3-aminoquinoline (**213**) in the synthesis of farnesyltransferase inhibitors **193** (Scheme 82).[124b] The drawbacks of this method are the low yields obtained for the hydrogenation and the products are formed racemically and, therefore, require a further chiral resolution step to obtain optically pure products.



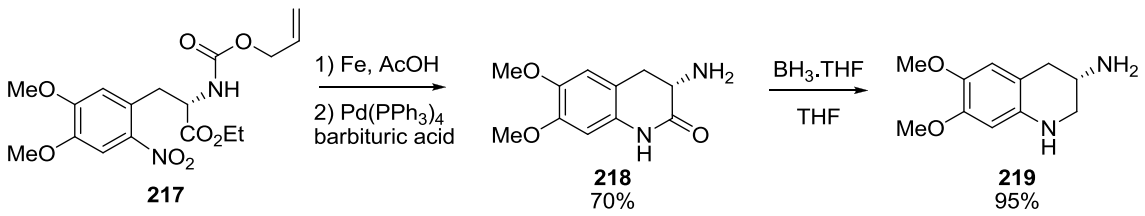
Scheme 82: Synthesis of 3-aminotetrahydroquinolines from 3-aminoquinolines.

The synthesis of (*S*)-903 (**192**) by Sudalai and co-workers was carried out using a $CoCl_2$-catalysed reductive cyclisation of nitro cyclic sulfite **214** (Scheme 83). The product tetrahydroquinolin-3-ol **215** was converted to 3-aminotetrahydroquinoline **192** by initial conversion to mesylate **216** and subsequent substitution with NaN_3 and hydrogenation.[123,131] This procedure benefitted from the use of a Sharpless asymmetric dihydroxylation (AD) to install the desired stereogenic centres.



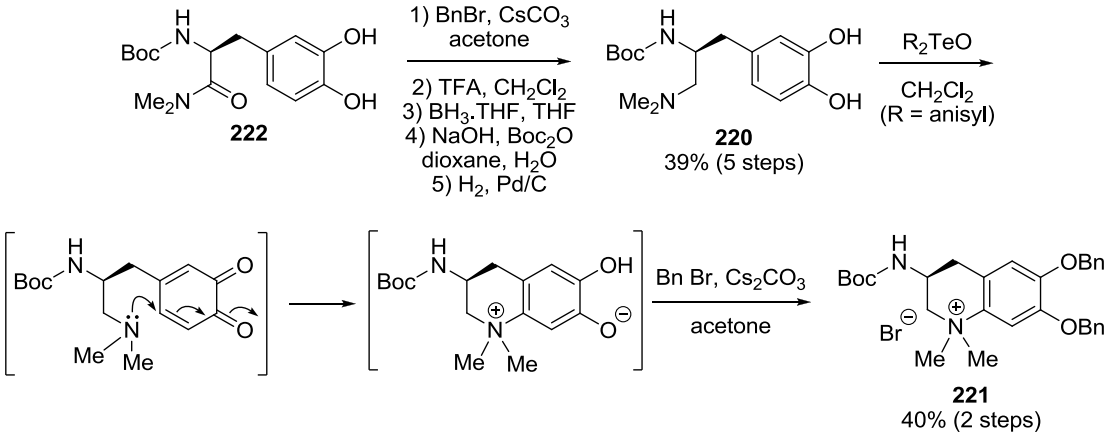
Scheme 83: Synthesis of 3-aminotetrahydroquinolines *via* reductive cyclisation of nitro cyclic sulfites **214**.

Many of the syntheses of 3-aminotetrahydroquinolines reported in the literature utilise a reduction of α-aminoamides to form the desired 1,2-diamine. The α-aminoamides are often readily available in enantiopure form from the corresponding amino acid derivatives. These reductions have been carried out both before and after cyclisation to form the tetrahydroquinoline ring. Gademann *et al.* used nitro-DOPA derivative **217** in a lactamisation reaction to form lactam **218**, which was subsequently reduced with borane to yield the desired 3-aminotetrahydroquinoline **219** (Scheme 84). This method was used in the synthesis of analogues of anachelin H (**188**).[132]



Scheme 84: Synthesis of 3-aminotetrahydroquinolines from cyclic α-aminoamides.

The same group also utilised an alternative method during the synthesis of anachelin H (**188**).[121c] They used a tellurium-mediated oxidative aza annulation of 1,2-diamine **220** to form **221**, the 3-aminotetrahydroquinoline fragment of anachelin H (**188**). Once again, they formed the 1,2-diamino moiety by reduction of an α-aminoamide (**222**) derived from DOPA, enabling the formation of **220** in enantiopure form (Scheme 85). This method demonstrates a new strategy towards the synthesis of these structures as it does not rely on the availability of substrates containing aromatic amine or nitro groups. The cyclisation is, however, limited to aromatic rings bearing the 1,2-dihydroxy groups, which are required for the reaction to proceed.



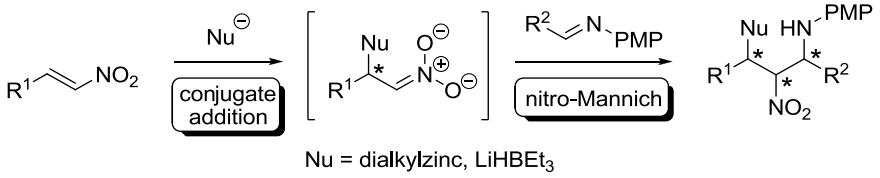
Scheme 85: Synthesis of 3-aminotetrahydroquinolines *via* a tellurium-mediated oxidative aza annulation.

The preceding sections in this thesis have detailed the importance of and methods available for the synthesis of 1,2-diamines. Particular attention has been paid to the nitro-Mannich reaction, which, as a result of recent advances in stereoselective methods and tandem processes, has become a highly attractive method for the synthesis of 1,2-diamines. The importance of 1,2-diamine-containing fused heterocyclic structures has also been highlighted. Current methods for the synthesis of such compounds have been discussed, many of which suffer from the disadvantage of requiring aromatic nitrogen functionalities, such as anilines or nitroarenes. The following sections will describe our recent work towards demonstrating the synthetic utility of the nitro-Mannich reaction through the synthesis of 1,2-diamine-containing fused heterocycles.

Chapter 2: *Results and Discussion*

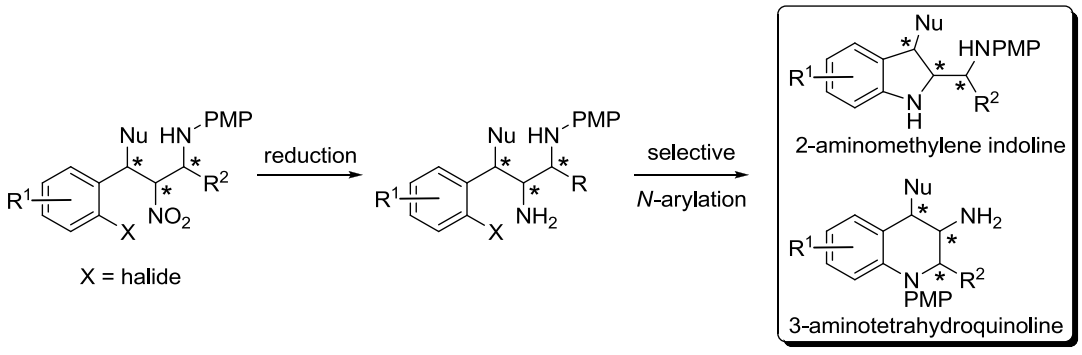
2.1 Proposed Research

As was discussed in the introductory chapter, the nitro-Mannich reaction is a versatile method for the synthesis of 1,2-diamines, which are important structures both biologically and synthetically. The conjugate addition nitro-Mannich procedures developed within our group have helped to overcome some of the limitations inherent in existing protocols, which often demonstrate limited scope with respect to the nitroalkanes used (Scheme 86).[105,106]



Scheme 86: Conjugate addition nitro-Mannich reactions.

We aim to demonstrate the synthetic utility of this reaction by utilising the *β*-nitroamine products in the synthesis of an array of fused nitrogen heterocycles bearing a 1,2-diamine. This would generate structures that could be of interest to both synthetic and medicinal chemists. The use of nitroalkenes in conjugate addition nitro-Mannich reactions provides ready access to *β*-nitroamine products with high levels of structural complexity, providing the opportunity for further manipulation to produce a range of useful intermediates. We envisaged the use of nitroalkenes bearing a pendant *ortho*-halo-aromatic group that could later be utilised in intramolecular *N*-arylation reactions to form a variety of fused heterocyclic structures. The presence of a 1,2-diamine provides the opportunity to perform selective *N*-arylation reactions to form both 2-aminomethylene indolines and 3-aminotetrahydroquinolines from a common precursor (Scheme 87). The following sections will describe the progress made towards this goal.

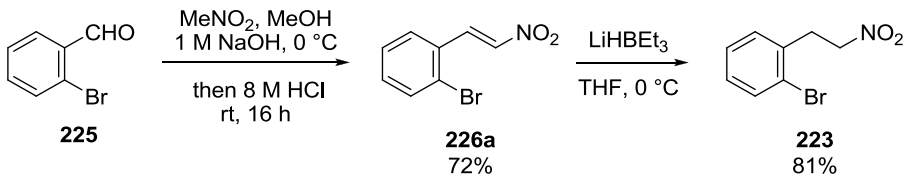


Scheme 87: Synthesis of 1,2-diamine containing fused heterocycles.

2.2 Nitro-Mannich Reactions

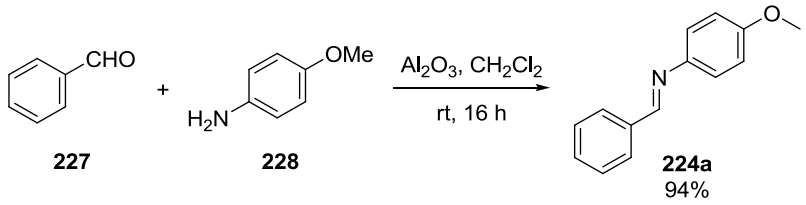
2.2.1 Base-Mediated Reactions

Investigations into the synthesis of the 1,2-diamine containing fused nitrogen heterocycles, as depicted in Scheme 87, began with the nitro-Mannich reaction. Previous studies within our group had shown that the $LiHBEt_3$-mediated reductive nitro-Mannich reaction gave poor results for nitroalkenes derived from benzaldehydes (see Scheme 74, section 1.5.2).[106] Initial studies into the nitro-Mannich reaction, therefore, began with the base-mediated nitro-Mannich reaction of nitroalkane **223** with PMP-phenylimine **224a**. The synthesis of nitroalkane **223** was accomplished using a Henry condensation reaction between 2-bromobenzaldehyde (**225**) and nitromethane,[97a] and subsequent reduction of 2-bromo-*β*-nitrostyrene (**226a**) with $LiHBEt_3$ (Scheme 88).[106]



Scheme 88: Synthesis of nitroalkane **223**.

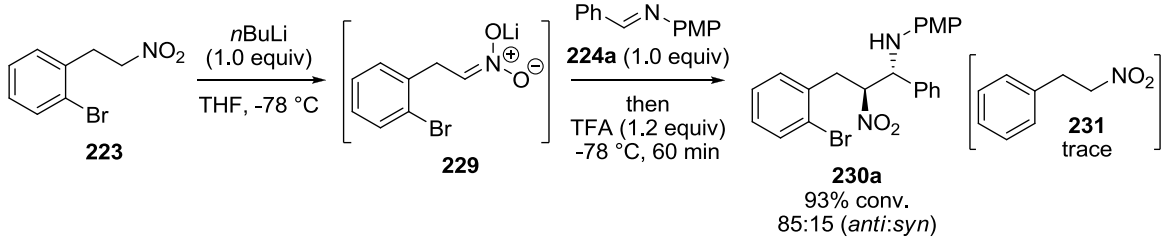
The PMP-phenylimine **224a** was formed by condensation of benzaldehyde (**227**) with *p*-anisidine (**228**) using alumina as a desiccant (Scheme 89).[53]



Scheme 89: Synthesis of *N*-PMP-phenylimine **224a**.

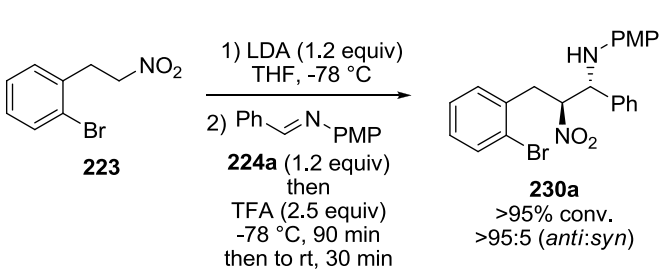
The nitro-Mannich reaction between nitroalkane **223** and PMP-phenylimine **224a** was first performed by deprotonation of the nitroalkane with *n*BuLi at -78 °C, to form nitronate **229**. Subsequent addition of imine **224a** and trifluoroacetic acid (TFA) promoted the desired reaction, forming *β*-nitroamine **230a** in >90% conversion after 60 min at -78 °C and with an *anti*:*syn* ratio of 85:15 (Scheme 90). The relative stereochemistry was assigned using ^1H NMR, by comparison of the coupling constants between the protons *α* to the nitro and amine groups, and was later confirmed by X-ray crystallography. The assignment of

relative stereochemistry is discussed in detail in Section 2.2.4. The desired product was accompanied by trace amounts of debrominated nitroalkane **231**, formed *via* halogen-lithium exchange and protonation of the resulting aryl-lithium species.



Scheme 90: Base mediated nitro-Mannich reaction with *n*BuLi.

It was thought that the use of an alternative weaker base would circumvent this debromination reaction. Therefore, the use of lithium diisopropylamide (LDA) for the formation of nitronate **229** was then investigated. Deprotonation of nitroalkane **223** was performed with 1.2 equiv. of freshly prepared LDA. After the sequential addition of imine **224a** and TFA at -78 °C the reaction was sampled at 30 min intervals and each sample, after aqueous workup, was immediately submitted for ^{1}H NMR analysis. The reaction with LDA proved to be slower than the reaction performed with *n*BuLi (see table in Scheme 91), however, the *anti*:*syn* ratio was consistently >95:5 for each sample taken. After 90 min at -78 °C the reaction was removed from the cold bath and allowed to warm to rt over 30 min. Complete conversion to *β*-nitroamine **230a** with >95:5 selectivity for the *anti* diastereomer (determined by ^{1}H NMR) was observed (Scheme 91). Furthermore, no formation of debrominated nitroalkane **231** was detected.



Time (min)	% conv.[a]
10	38 (55)
30	59 (82)
60	68 (92)
90	77 (93)
120[b]	>95 (93)

[a] number in parenthesis shows result from reaction with *n*BuLi.
[b] reaction removed from the cold bath after 90 min.

Scheme 91: Base mediated nitro-Mannich reaction with LDA.

The purification of *β*-nitroamine **230a** by column chromatography was problematic due to its instability, resulting from a retro-addition process to reform nitroalkane **223** and imine **224a**. Purification was further complicated by the presence of imine **224a**, which undergoes hydrolysis during chromatography preventing efficient separation from the desired product.

Nonetheless, isolation of **230a** was achieved in 72% yield with approximately 80% purity (4:1 ratio of **230a**:**224a**). Although relatively unstable in solution, *β*-nitroamine **230a** was found to be a stable solid, forming bright yellow crystals. Crystallisation by slow evaporation of Et_2O enabled confirmation of the relative stereochemistry by single crystal X-ray crystallography (Figure 14).

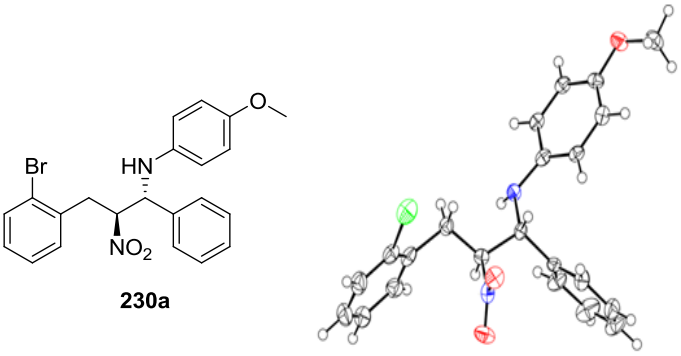


Figure 14: X-ray crystal structure of *β*-nitroamine **230a**.

2.2.2 Isolation of Nitro-Mannich Products

Isolation of the products of nitro-Mannich reactions can prove to be problematic due to a retro-addition reaction, which can lead to reduced yields and erosion of diastereoselectivity. Methods that have been used previously in our group to overcome this problem include reduction of the nitro group to form the more stable 1,2-diamines,[41] or protection with trifluoroacetic anhydride (TFAA) to form *β*-nitrotrifluoroacetamides.[105] The latter prevents retro-addition by delocalisation of the nitrogen lone pair into the amide bond (Figure 15).

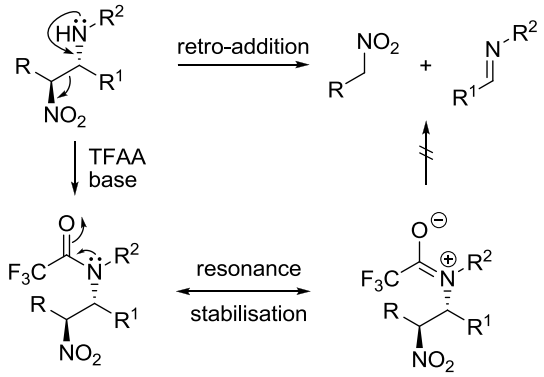
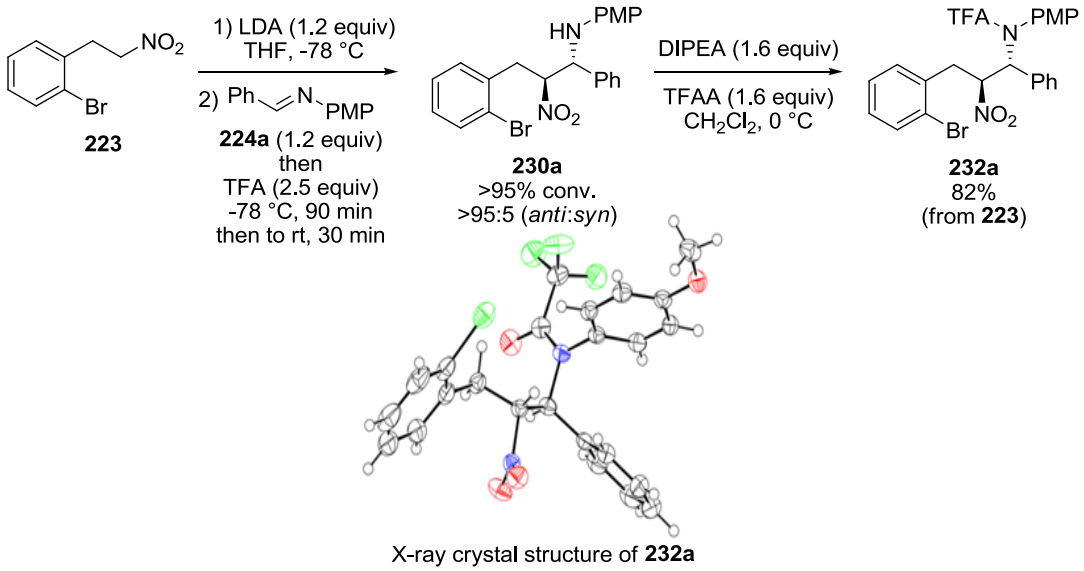


Figure 15: Retro-addition mechanism and amide stabilisation.

Over the course of the research conducted towards this thesis both the reduction and protection of *β*-nitroamine **230a** were investigated. The reduction of *β*-nitroamines and

β-nitroacetamides will be discussed in detail later. The current section will focus on the formation of *β*-nitroacetamides through protection with TFAA.

The protection of *β*-nitroamine **230a** was performed on the crude nitro-Mannich mixture, thereby preventing any degradation that may occur during purification. Treatment of crude *β*-nitroamine **230a**, formed using the LDA-mediated nitro-Mannich reaction, with TFAA and diisopropylethylamine (DIPEA) promoted the desired protection, forming *β*-nitroacetamide **232a** in 82% yield over two steps (Scheme 92). No epimerisation was observed during the reaction and the relative stereochemistry was again confirmed by single crystal X-ray crystallography. Furthermore, separation of **232a** from the excess imine **224a** was aided by the complete degradation of **224a** during the reaction, forming benzaldehyde and *N*-PMP-trifluoroacetamide.



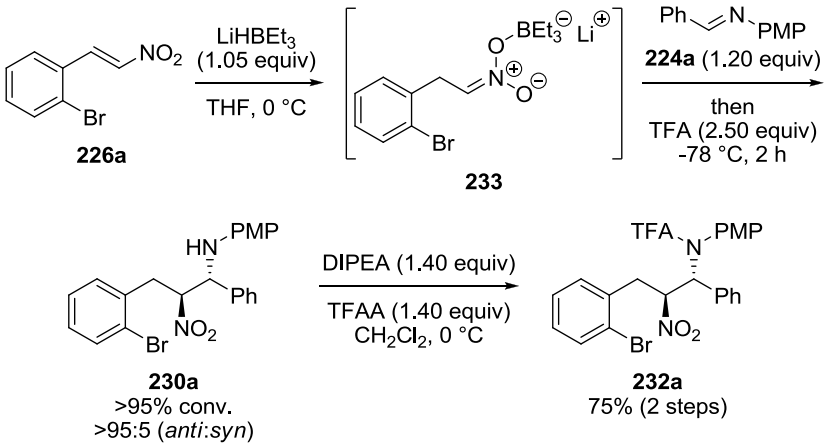
Scheme 92: Formation of *β*-nitroacetamide **232a**.

The protection with TFAA occurs rapidly, even at low temperatures, and allows the easy isolation of the nitro-Mannich products while minimising the amount of retro-addition that might occur. Furthermore, the crystalline nature of these compounds allows their isolation in high levels of purity and provides the opportunity for recrystallisation to improve the diastereoselectivity of the products, which is important if insufficient diastereoselectivity is achieved in the nitro-Mannich reaction or separation of the diastereomers is not possible using column chromatography.

2.2.3 Reductive Nitro-Mannich Reaction

As was mentioned in the introductory chapter, previous studies within the group have shown that the $LiHBEt_3$-mediated reductive nitro-Mannich reaction performed well with nitroalkenes derived from aliphatic aldehydes but gave poor results for nitroalkenes derived from benzaldehydes (see Scheme 74, section 1.5.2).[106] As the nitro-Mannich reaction used for our synthesis required the nitroalkene derived from 2-bromobenzaldehyde it was initially thought that this substrate would also perform poorly in the reductive nitro-Mannich reaction. However, previous reductive nitro-Mannich reactions utilised *N*-OMB-imines with AcOH as the proton source. Subsequent studies into conjugate addition nitro-Mannich reactions have shown that *N*-PMP-imines provide higher levels of diastereoselectivity, and that the use of the stronger acid TFA is more effective at promoting the nitro-Mannich reaction.[105] It was postulated that the reductive nitro-Mannich reaction would also benefit from the use of *N*-PMP-imines and TFA.

Initial attempts towards a reductive nitro-Mannich reaction between nitroalkene **226a** and imine **224a** were performed by treatment of the nitroalkene with 1.05 equiv. of $LiHBEt_3$ to form nitronate **233**, which precipitated from the reaction mixture as a white solid. Cooling this heterogeneous mixture to -78 °C followed by addition of imine **224a** and TFA promoted the desired nitro-Mannich reaction which formed a yellow homogeneous solution. The reaction provided *β*-nitroamine **230a** in >95% conversion after 2 h at -78 °C and with an *anti*:*syn* ratio of >95:5. Protection with TFAA furnished *β*-nitroacetamide **232a** in 75% yield over two steps (Scheme 93). Subsequent experiments showed the nitro-Mannich reaction to reach >90% conversion after 15 min at -78 °C, with complete conversion being achieved after 60 min at -78 °C.



Scheme 93: Reductive nitro-Mannich reaction.

This reductive nitro-Mannich reaction provides a significant improvement to the base-mediated nitro-Mannich reaction shown in Scheme 92, with *β*-nitroacetamide **232a** being formed in 75% overall yield from nitroalkene **226a**, compared to 66% for the base-mediated procedure. It is also more operationally simple as it eliminates the need to isolate and purify the nitroalkane **223** and does not require the formation of LDA.

The drastic increase in efficiency observed when using *N*-PMP-imines and TFA, compared to *N*-OMB-imines and AcOH, is thought to be due to the effect of the acids on the solubility of nitronate **233** in THF. Upon treatment of nitroalkene **226a** with $LiHBEt_3$, nitronate **233** precipitates from the reaction mixture as a white solid, an effect that was not observed when using nitroalkenes derived from aliphatic aldehydes.[106] This poor solubility necessitates the addition of a strong acid, such as TFA (pK_a 0), to solubilise nitronate **233**, presumably by reaction to form a nitronic acid or by modification of the boron species. Once a homogeneous reaction mixture is formed the desired nitro-Mannich reaction can occur. Protonation of nitronate **233** with the less acidic AcOH (pK_a 5) is slower, so a heterogeneous reaction mixture remains and leads to poor conversion to the *β*-nitroamine products. Elevated temperatures and prolonged reaction times result in the competing retro-addition reaction, which prevents any improvement to the conversions. The beneficial effect of using *N*-PMP-imines over the *N*-OMB-imines is also evident as improvements in diastereoselectivities are observed. This is believed to be a result of the different basicities of the nitrogen atoms of each imine, with the *N*-PMP-imine (pK_a ~3) being less basic than the *N*-OMB-imine (pK_a ~7). The lower basicity results in a slower and more selective reaction. The greater conformational rigidity of the *N*-PMP-imines compared to the *N*-

OMB-imines could also have an effect, with reduction in the degrees of freedom in the transition state leading to improved selectivities. Finally, the improved stability of the *N*-PMP-*β*-nitroamine products compared to the *N*-OMB-products could minimise the amount of retro-addition occurring in the reaction, providing higher conversions and diastereoselectivities. This improved stability arises from the lower basicity of the PMP protected amine which, as a result of partial delocalisation into the phenyl ring, causes a reduction in the availability of the nitrogen lone pair to undergo the retro-addition process.

2.2.4 Origin of Diastereoselectivity

The origin of the diastereoselectivity in the nitro-Mannich reaction is believed to arise from a hydrogen bonded Zimmer-Traxler-type chair transition state (TS).[41] Due to the imine being fixed in an *E*-configuration, the favoured TS is one that minimises the 1,3-diaxial interaction between the large PMP group and the nitronate substituent. This is the case in the TS leading to the *anti*-product, which is believed to be the kinetic product of the reaction (Figure 16). The TS leading to the *syn*-product is disfavoured due to unfavourable 1,3-diaxial interactions between the PMP and R^1 groups. The *syn*-product is believed to be the thermodynamic product as it can adopt a hydrogen-bonded six-membered ring conformation with all substituents in *pseudo*-equatorial positions, unlike the *anti*-product. Indeed, previous observations have confirmed that epimerisation of the kinetic *anti*-product to the thermodynamic *syn*-product occurs on standing in solution, proceeding *via* a retro-nitro-Mannich/nitro-Mannich process.[105]

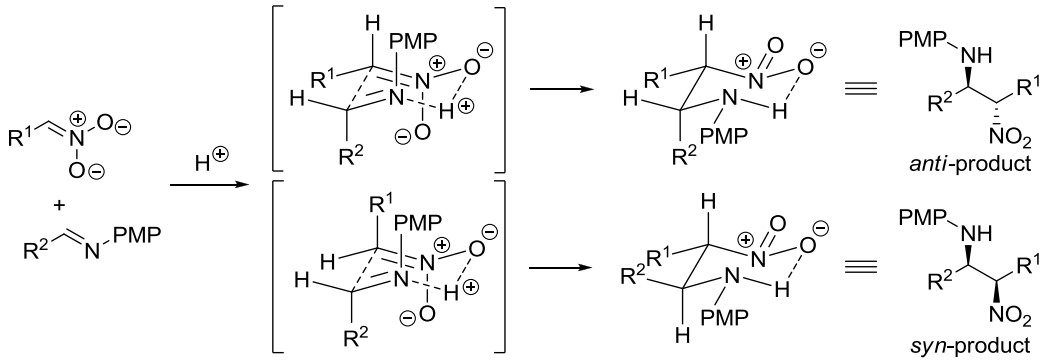


Figure 16: Origin of diastereoselectivity.

The tendency of *β*-nitroamines to adopt hydrogen-bonded six-membered rings enables the assignment of their relative stereochemistry using ^{1}H NMR. This approach was originally employed by Seebach *et al.* in their work on diastereoselective nitroaldol (Henry) reactions.[133] They postulated that the more highly populated conformations of *β*-nitroalcohols are those that exhibit a hydrogen bond between the vicinal O–H and ON–O groups. As a result, the coupling constants between the protons *α* to these groups could be used to determine the relative stereochemistry. By analogy, the coupling constants between the protons *α* to the nitro and amine groups in *β*-nitroamines can be used to determine relative stereochemistry, with the axial-axial coupling larger than the axial-equatorial coupling (Figure 17).[41] This analysis was used in the assignment of the relative stereochemistry of all subsequent reductive nitro-Mannich products and was supported by X-ray crystal analysis of several products.

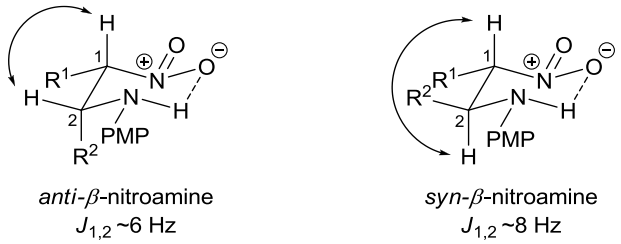


Figure 17: Origin of diastereoselectivity.

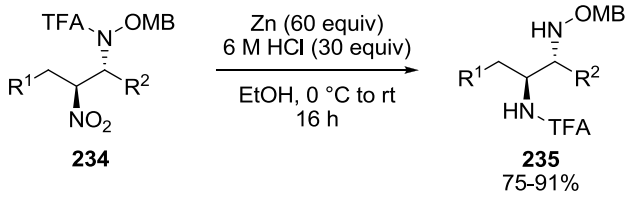
With the nitro-Mannich products *β*-nitroamine **230a** and *β*-nitroacetamide **232a** formed in high yield and excellent diastereoselectivity, attention was then turned to the reduction of the nitro group to form the desired 1,2-diamine products. The methods investigated to promote this transformation will be discussed in the following section.

2.3 Reduction to 1,2-Diamines

As was discussed in section 1.4.1, the reduction of nitro groups is an important method for the synthesis of amines. This highly valuable transformation has also been successfully applied to the synthesis of 1,2-diamines *via* reduction of the *β*-nitroamine products of nitro-Mannich reactions. The synthesis of the 1,2-diamines required for use in our intramolecular *N*-arylation reactions could be performed by reduction of either *β*-nitroamine **230a** or *β*-nitroacetamide **232a**. Similar reductions have been successfully carried out previously within our group but certain differences between substrates meant that complications could arise. Most importantly, the reduction of a *β*-nitroamine in the presence of an aromatic bromide had not previously been performed. This could be problematic due to the lability of aromatic halides under standard reducing conditions, such as hydrogenations. The optimisation studies that were carried out to affect the reduction of *β*-nitroamine **230a** and *β*-nitroacetamide **232a** are discussed in the following sections.

2.3.1 Reduction of *β*-Nitroacetamides

Previous work within our group has shown that *β*-nitroacetamides **234** could be effectively reduced using a Zn/HCl reduction (Scheme 94). The reactions yielded the orthogonally protected 1,2-diamines **235** in excellent yield, formed by transacylation of the trifluoroacetyl protecting group to the newly formed primary amine.[106]

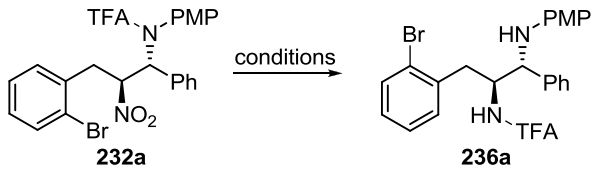


Scheme 94: Previous reductions of nitro-Mannich products.

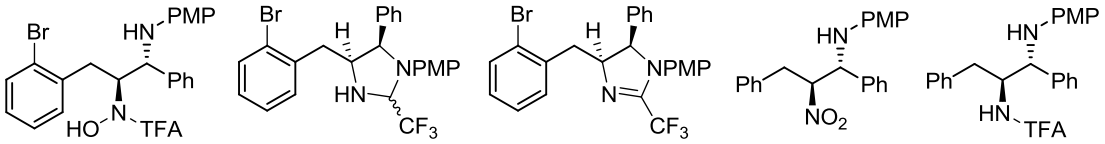
There are, however, a number of important differences between the systems shown in Scheme 94 and *β*-nitroacetamide **232a** that could potentially affect the efficiency of the reduction. The use of the PMP protecting group, which will affect the nucleophilicity of the protected amine and could have possible consequences with regards to the transacylation

process; and the presence of the aromatic bromide may cause problems, as was mentioned previously. Considering these differences, the reduction of *β*-nitroacetamide **232a** was attempted using the same conditions. The results of the optimisation studies for the reduction of *β*-nitroacetamide **232a** are given in Table 1.

Initial attempts at the reduction of *β*-nitroacetamide **232a** with the conditions demonstrated in Scheme 94 gave a very low yield (<10%) of the desired 1,2-diamine **236a**, accompanied by a number of other products (Table 1, entry 1). These included hydroxylamine **237**, formed by under-reduction, and imidazolidine **238** (2:1 dr), formed by an intramolecular condensation of the amine and trifluoroacetyl groups of 1,2-diamine **236a** and subsequent reduction of the product dihydroimidazole **239**. The reduction was also initially attempted with several other protocols. Hydrogenation over Pd/C gave no observed reduction of the nitro group but resulted in complete debromination within 15 h at rt under 1 bar of H_2 to give *β*-nitroacetamide **240** (Table 1, entry 2).[134] The use of Raney nickel and N_2H_4 gave no desired product and formed only trace amounts of hydroxylamine **237** (Table 1, entry 3).[135] Nickel boride resulted in complete reduction of *β*-nitroacetamide **232a** but with the debrominated diamine **241** formed as the major product (Table 1, entry 4).[136] Although the Zn/HCl reduction protocol gave only a low yield of the desired product, the stability of the aromatic bromide under the reaction conditions prompted further optimisation studies. Increasing the equivalents of both Zn and HCl increased the amount of reduction of hydroxylamine **237** but resulted in formation of imidazolidine **238** (2.5:1 dr) as the major product (Table 1, entry 5). It was found that using an excess of HCl with respect to Zn greatly reduced the amount of imidazolidine **238** that was formed, instead giving rise to larger amounts of dihydroimidazole **239** and the desired product **236a** (Table 1, entries 6-9). Complete reduction of hydroxylamine **237** was accomplished by addition of the Zn in two portions, although the additional zinc resulted in the formation of small amounts of debrominated product **241** (Table 1, entry 10). The optimum conditions were found to be with 75 equiv. of Zn, added in two portions, and 250 equiv. of 6 M HCl performed in a mixed solvent system of EtOH and EtOAc. The addition of EtOAc aided solubilisation of the reactants and enabled the reactions to be conducted at a higher concentration. It was found that hydrolysis of dihydroimidazole **239** could be accomplished by treatment of the crude product with 6 M HCl in EtOH/EtOAc. This provided near quantitative conversion to diamine **236a** and resulted in a purified yield of 89% (Table 1, entry 11).



232a **236a**



237 **238** **239** **240** **241**

Entry	Conditions	Conversion (%)[a]					
		236a	**237**	**238**	**239**	**240**	**241**
1	Zn (60 equiv), 6 M HCl (30 equiv), EtOH	9	53	38	0	0	0
2	H_2, Pd/C, MeOH	0	0	0	0	100	0
3	Raney Ni/N_2H_4	0	0	0	0	0	<5
4	$NiCl_2.6H_2O$, $NaBH_4$, MeOH	35	21	0	2	0	43
5	Zn (80 equiv), 6 M HCl (40 equiv), EtOH	32	19	48	1	0	0
6	Zn (60 equiv), 6 M HCl (100 equiv), EtOH	62	28	1	9	0	0
7	Zn (60 equiv), 6 M HCl (200 equiv), EtOH	74	13	0	13	0	0
8	Zn (60 equiv), 6 M HCl (300 equiv), EtOH	67	13	0	20	0	0
9	Zn (100 equiv), 6 M HCl (300 equiv), EtOH	62	8	0	25	0	5
10[b]	Zn (75 equiv), 6 M HCl (300 equiv), EtOH	78	0	0	16	0	6
11[b,c]	Zn (75 equiv), 6 M HCl (250 equiv), EtOH, EtOAc	95 (89)	0	0	0	0	5

[a] Determined by ^{1}H NMR. Numbers in parenthesis show purified yield. [b] Zinc added in two portions (50 equiv and 25 equiv). [c] Crude product treated with 6 M HCl (20 equiv) in EtOH for 1 h.

Table 1: Optimisation of nitro reduction.

Several points should be taken into consideration when describing the Zn/HCl reduction of *β*-nitroacetamide **232a**. Firstly, the large excess of Zn and HCl required for the reduction to reach completion and, secondly, the reasons for the formation of the dihydroimidazole and

imidazolidine products **238** and **239**, which were not observed during the reduction of OMB-analogues **234** (see Scheme 94).

The large excess of zinc and acid required for complete reduction of the nitro group results from the difficulty in reducing the hydroxylamine intermediate **237**. The mechanism proceeds *via* a single electron transfer process with nitroso and hydroxylamine intermediates, and requires 6 equiv. of both Zn and HCl (Figure 18). It was confirmed that the transacylation process occurs either prior to or at the hydroxylamine stage of the reduction by isolation and characterisation of a hydroxylamine intermediate.[106] The partial reduction of the nitro group to the hydroxylamine was shown to proceed with as little as 10 equiv. of Zn, and it was only after the transacylation process occurred that the rate of reduction decreased significantly. This dramatic decrease in reduction rate caused by the presence of the trifluoroacetyl group was later highlighted during the reduction of non-TFA-protected products, which could be carried out with as little as 10 equiv. of Zn (see section 2.5.2).

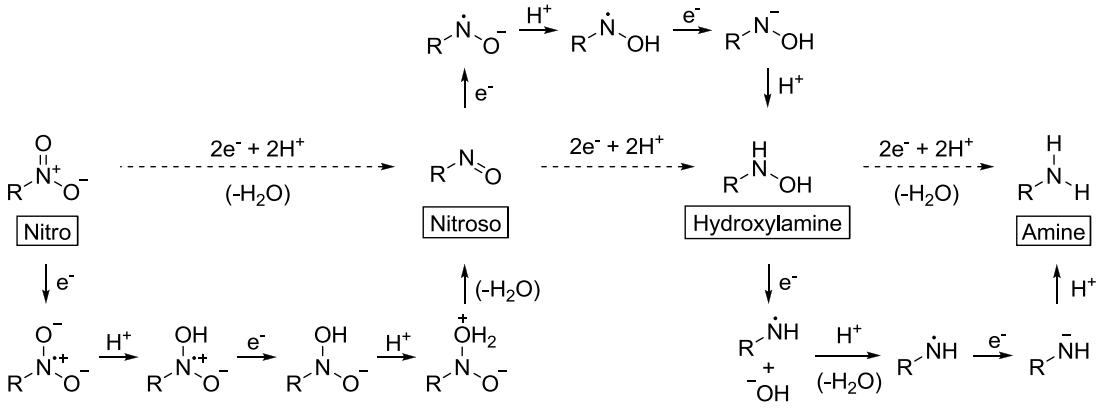
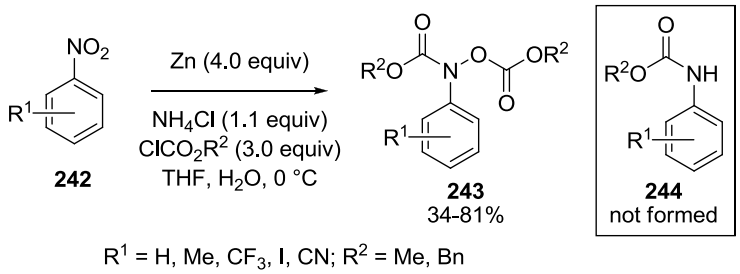


Figure 18: Mechanism of Zn/HCl reduction.

The observed decrease in the rate of reduction of acyl-protected hydroxylamines is in agreement with the work completed by the group of Tomkinson, who performed reductive acylations of nitroarenes **242** to synthesise *N*,*O*-bisacylated hydroxylamines **243** (Scheme 95).[137] Carrying out the Zn-mediated nitro reduction in the presence of an excess of methyl or benzyl chloroformate trapped the *N*-aryl hydroxylamine intermediates and prevented over reduction to the *N*-acylated anilines **244**. In our system, as in that reported by Tomkinson *et al.*, the presence of the carbonyl protecting group slows the rate of transfer of

an electron from Zn to the hydroxylamine intermediate. As a result, more forcing conditions must be used to affect complete reduction to the protected amine.



Scheme 95: Reductive acylation of nitroarenes.

The observed formation of imidazolidine **238** and dihydroimidazole **239** during the reduction of PMP-*β*-nitroacetamides but not OMB-*β*-nitroacetamides could be explained by the lower basicity of the PMP-amines (pK_a ~5) compared to the OMB-amines (pK_a ~9).[138] These differences in basicity will dictate which nitrogen is protonated during the transacylation process and, as a result, which products are formed. A plausible mechanism that can be used to rationalise these observations is given in Figure 19. Initially, intramolecular nucleophilic attack of the trifluoroacetamide by the hydroxylamine results in the formation of aminal **245**. Under the acidic reaction conditions protonation of aminal **245** can occur either at the hydroxylamine to give **246** or at the protected amine to give **247**, with an equilibrium existing between these two species. The position of this equilibrium is dependent on the basicity of the two nitrogen centres, and as the hydroxylamine nitrogen has a pK_a of ~6 the position will be affected by the amine protecting group (R). When R = PMP the protected nitrogen has a pK_a of ~5 so the equilibrium favours **246**, whereas when R = OMB the protected nitrogen has a pK_a of ~9 resulting in the equilibrium shifting in favour of **247**. When the equilibrium favours **247** the subsequent formation of the desired transacylated product **248** is fast, as is the case when R = OMB. When R = PMP the rate of formation of **247** is reduced resulting in a competing pathway involving loss of water to give carbocation **249**, which can then be rapidly reduced to give dihydroimidazole **250**. As only small amounts of dihydroimidazole **250** (10-20%) were observed in the crude reaction mixtures the loss of water from **246** to give **249** must be relatively slow. However, once formed dihydroimidazole **250** is stable under the reaction conditions and requires an additional acid hydrolysis after the initial work up to convert into diamine **248**.

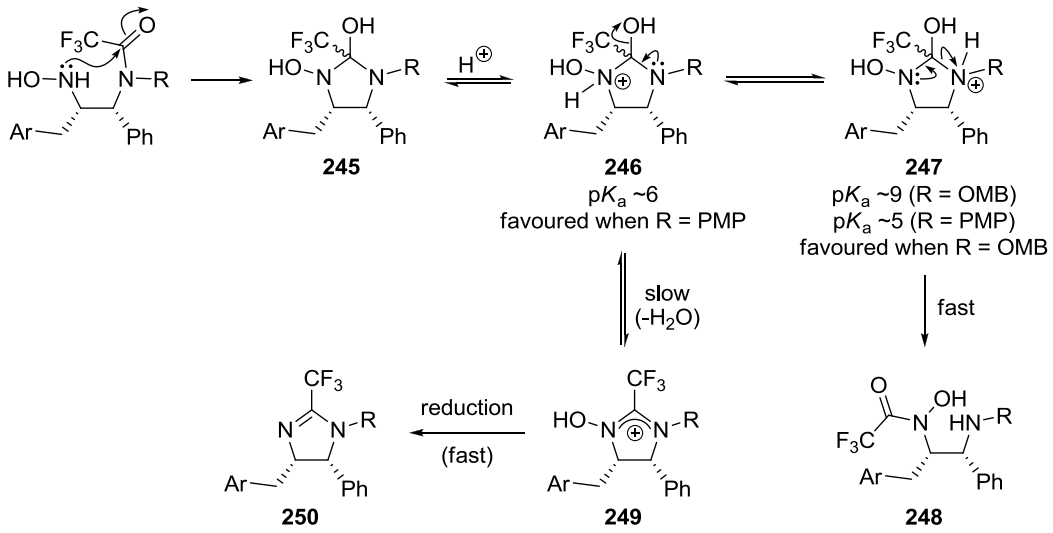
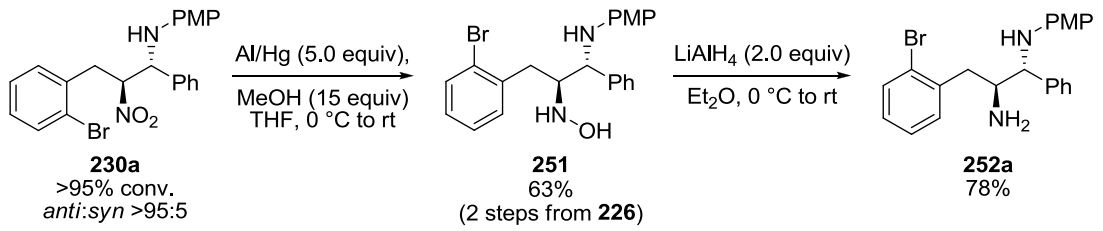


Figure 19: Transacylation mechanism.

2.3.2 Reduction of *β*-Nitroamines

As was mentioned previously, the reduction of unprotected *β*-nitroamines has also been successfully carried out. One particular method that has proved to be successful for the reduction of unstable *β*-nitroamines is the use of aluminium amalgam (see Scheme 55, section 1.4.1).[84] This method proceeds *via* initial formation of the hydroxylamine intermediate, which is subsequently reduced by either hydrogenation or treatment with $LiAlH_4$. As the aromatic bromide in *β*-nitroacetamide **232a** has already been shown to be unstable under hydrogenation conditions, only the use of $LiAlH_4$ to reduce the hydroxylamine intermediate was investigated.

It was found that treatment of crude *β*-nitroamine **230a** with 5.0 equiv. of freshly amalgamated aluminium foil in the presence of 15 equiv. of MeOH promoted the desired reduction. Hydroxylamine **251** was formed in 63% over two steps from nitroalkene **226a** (Scheme 96). Subsequent reduction with $LiAlH_4$ provided mono-protected diamine **252a** in 78% yield.

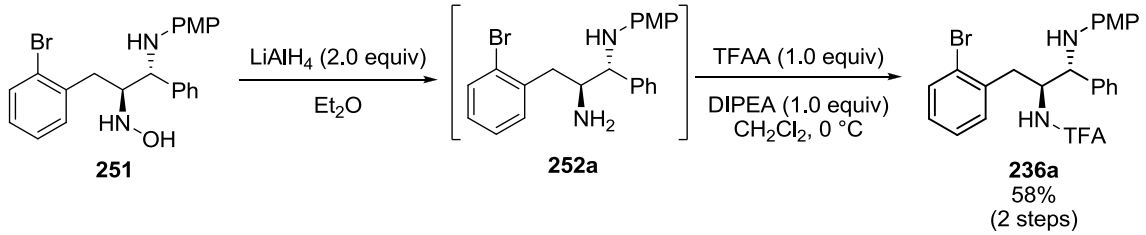


Scheme 96: Reduction of unprotected nitro-Mannich product.

As the aim of this research is to synthesise an array of analogous fused heterocyclic products this reduction protocol provides a useful alternative route to the desired 1,2-diamines, should any analogues be incompatible with the Zn/HCl method. Certain drawbacks, however, do exist within this method. These include the use of highly toxic mercury reagents, which require careful handling and disposal; the lower yields obtained, with diamine **252a** being formed in 49% overall yield compared to 69% for **236a**; and the difficulty in purifying diamine **252a**, which was problematic due to the tendency of impurities to co-run with the desired product.

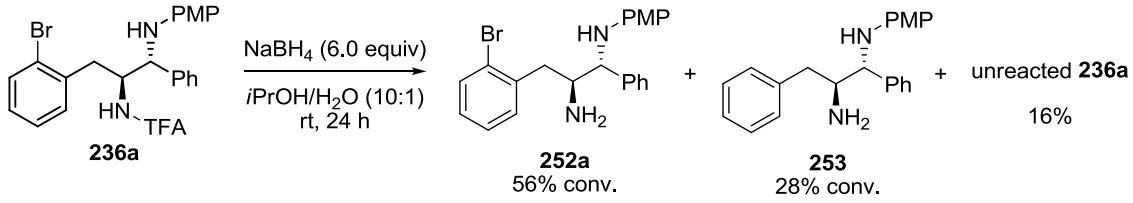
2.3.3 Protection/Deprotection of 1,2-Diamines

To enable the use of both the Zn/HCl and Al/Hg/$LiAlH_4$ reduction protocols it was necessary to be able to readily convert between the mono-protected diamine **252a** and the TFA-protected diamine **236a**. To enable this, we required suitable protection and deprotection protocols. The protection of mono-protected diamine **252a** proved to be straightforward and could be achieved by treatment of crude **252a** with an equivalent of TFAA and DIPEA. The TFA-protected product **236a** was isolated in 58% yield over the two steps (Scheme 97).



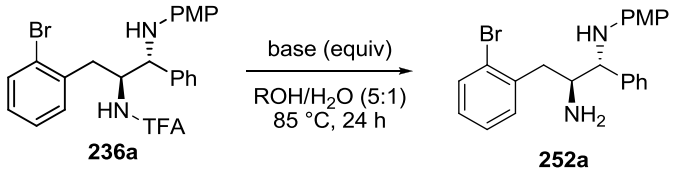
Scheme 97: TFA protection of diamine **252a**.

Removal of the TFA group, to form diamine **252a** from **236a**, proved less straightforward and required optimisation. Initially the use of $NaBH_4$ was attempted (Scheme 98).[139] This resulted in 84% removal of the TFA group from diamine **236a**, but the desired product was unexpectedly accompanied by 28% of debrominated diamine **253**. As the formation of debrominated product **253** should not be possible under these reaction conditions it may have resulted from the action of transition metal contaminants in the reaction. In the presence of $NaBH_4$, these could form transition metal borides that can cause dehalogenation (for an example, see entry 4, Table 1). Although further investigations are required to determine the cause of this reaction, as separation of the desired product from the debrominated impurity was not possible by column chromatography alternative deprotection methods were investigated.



Scheme 98: Attempted TFA deprotection of diamine **252a**.

The use of K_2CO_3 in refluxing aqueous MeOH gave a much more promising result.[140] With 5.0 equiv. of K_2CO_3 85% conversion of diamine **236a** was achieved after 24 h, providing diamine **252a** in 61% isolated yield (Table 2, entry 1). This prompted a screen of different bases in either aqueous MeOH or EtOH, the results of which are shown in Table 2. Increasing the amount of K_2CO_3 to 10 equiv. improved the conversion to 94%, whereas performing the reaction in EtOH reduced the rate of deprotection to give only 48% conversion (Table 2, entries 2 and 3). The use of Na_2CO_3 gave much lower conversions in both MeOH and EtOH (Table 2, entries 4 and 5). It was found that hydroxide bases, unlike the carbonate bases, gave better conversions in EtOH than in MeOH and complete conversion was observed when using NaOH in EtOH, although an isolated yield of only 66% was obtained (Table 2, entry 7). The base of choice was found to be KOH which gave complete conversion with an isolated yield of 86% (Table 2, entry 9). The yield was increased to 94% through the use of 15 equiv. of KOH and by reducing the reaction time to 6 h (Table 2, entry 10). It is possible that the prolonged reaction times caused partial degradation of diamine **252a** resulting in reduced yields.



236a **252a**

Entry	Base (equiv)	ROH	Conversion (%)[a]
1	K_2CO_3 (5.0)	MeOH	85 (61)
2	K_2CO_3 (10)	MeOH	94
3	K_2CO_3 (10)	EtOH	48
4	Na_2CO_3 (10)	MeOH	30
5	Na_2CO_3 (10)	EtOH	14
6	NaOH (10)	MeOH	75
7	NaOH (10)	EtOH	100 (66)
8	KOH (10)	MeOH	74
9	KOH (10)	EtOH	100 (86)
10[b]	KOH (15)	EtOH	100 (94)

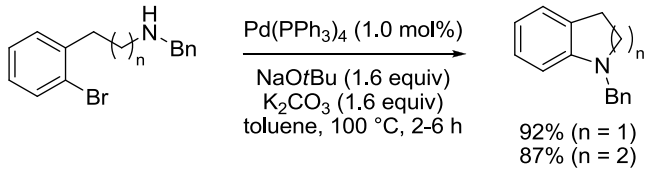
[a] Determined by ^{1}H NMR. Numbers in parenthesis show purified yield. [b] Reaction heated for 6 h.

Table 2: Optimisation of TFA deprotection.

The use of this TFA deprotection procedure allowed the formation of mono-protected diamine **252a** in 68% overall yield from nitroalkene **226a**. This is a marked improvement on the Al/Hg/$LiAlH_4$ method, which gives an overall yield of 49%. With convenient and high yielding syntheses of diamines **236a** and **252a** in hand, investigations into the intramolecular *N*-arylation reactions for the synthesis of fused heterocyclic products were undertaken.

2.4 Intramolecular *N*-Arylations

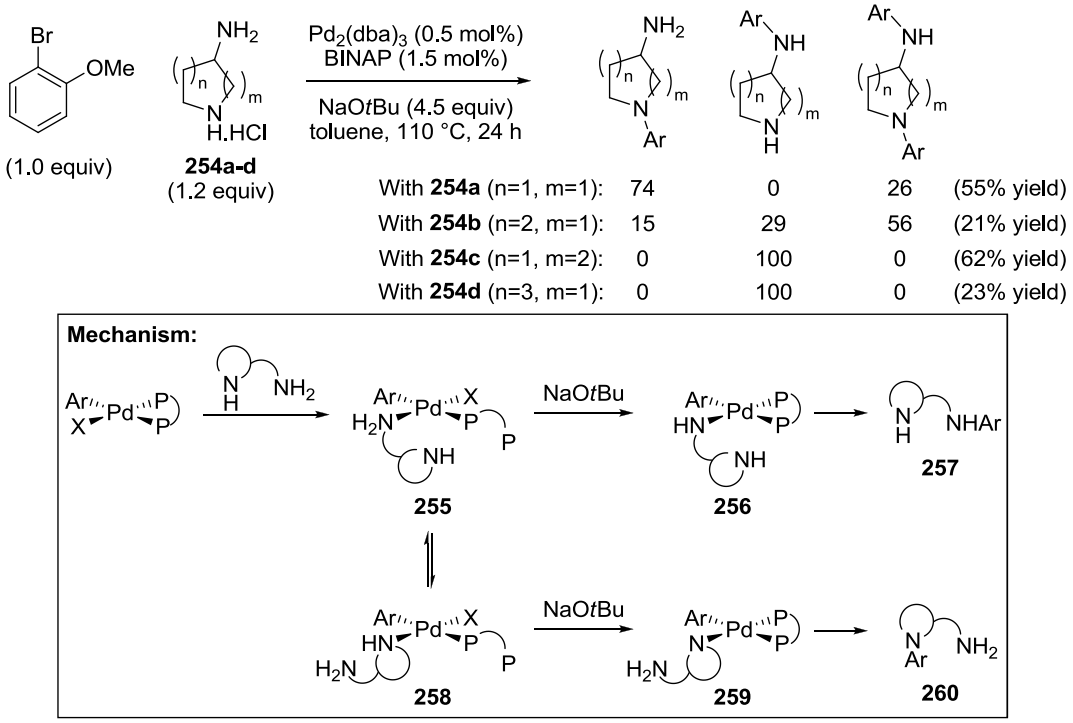
The palladium catalysed coupling of amines with aromatic halides, known as the Buchwald-Hartwig reaction has become a highly useful method from the synthesis of aromatic amines.[141] The intramolecular version of this reaction has been successfully applied to the synthesis of both five- and six-membered ring heterocycles.[142] An example is the work performed by Buchwald *et al.* who showed that $Pd(PPh_3)_4$ is an effective catalyst for the synthesis of simple indolines and tetrahydroquinolines (Scheme 99).[142a]



Scheme 99: Intramolecular *N*-arylations.

The selective mono-arylation of poly- and diamines has also been reported in the literature, although this has mainly been limited to intermolecular examples.[143] One such example is a study performed by Rouden *et al.* They investigated the effect of the ring size of cyclic secondary amines bearing a pendant primary amine on the chemoselectivity of *N*-arylations. They found that the chemoselectivity of the reaction was dependent on the ligand (steric and electronic factors), the aryl halide, the ring size of the substrate, and its coordination characteristics. Less flexible diamines, such as the five-membered ring compound **254a**, underwent arylation almost exclusively at the secondary amine, whereas the six-membered ring diamines **254b** and **254c** favoured arylation at the primary amine, although modulation of selectivity was possible using different ligands and/or aryl halides. The larger and more flexible seven-membered ring diamine **254d** was found to undergo arylation almost exclusively at the primary amine (Scheme 100).[143g] They rationalised these observations by describing an equilibration between coordination of the primary and secondary amines of diamines **254** to the palladium centre during the catalytic cycle (see mechanism in Scheme 100). Initial coordination of the primary amine occurs preferentially due to the steric constraints of the secondary amine, forming complex **255**. The addition of a base then generates Pd-amido complex **256**, which can undergo reductive elimination to give arylation of the primary amine (product **257**). With flexible diamines **254b-d** arylation of the primary amine is favoured because the formation of Pd-amido complex **256** occurs

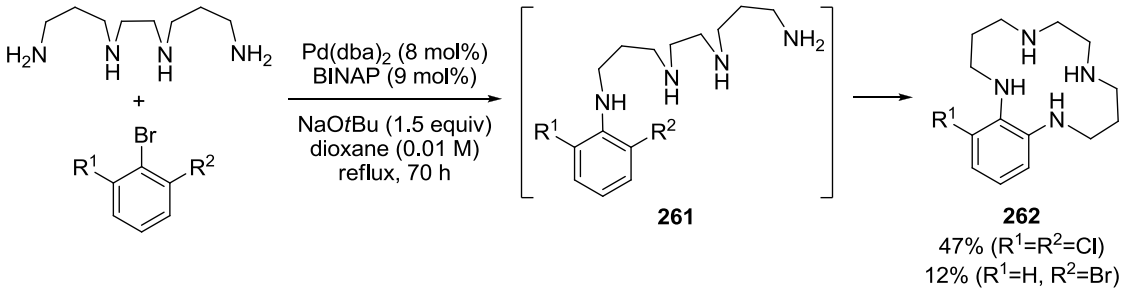
faster than equilibration to **258**. Conversely, when five-membered ring diamine **254a** is used its restricted conformation forces the proximity of the secondary amine to the metal centre in complex **255**. This could, therefore, shift the equilibrium position to favour complex **258**. Once this complex is generated reaction to form Pd-amido complex **259** should occur faster than that to form Pd-amido complex **256**. This is because reductive elimination yielding product **260** is more facile because of the steric constraint introduced by the secondary amine at the metal centre and the higher nucleophilicity of the secondary amine group.



Scheme 100: Chemoselective intermolecular *N*-arylations.

Although the intermolecular selective mono-arylation of poly- and diamines has been investigated,[143] intramolecular examples are far less common and have mainly been applied to the formation of polyazamacrocycles in low to moderate yields.[144] An example is given by the group of Beletskaya who synthesised a variety of nitrogen analogues of benzocrown ethers using the Pd-catalysed amination of di- and tri-haloarenes with linear polyamines (Scheme 101).[144b] The reactions proceed *via* initial intermolecular *N*-arylation, forming linear product **261**, and subsequent intramolecular *N*-arylation to give the macrocyclic product **262**. Both reactions give high selectivity for reaction at primary amines. The reactions of trihaloarenes gave higher yields of the macrocyclic products than dihaloarenes

as, after the initial intermolecular *N*-arylation, the electron withdrawing influence of the second halogen in **261** decreases the unfavourable mesomeric donor influence of the first introduced amino group.



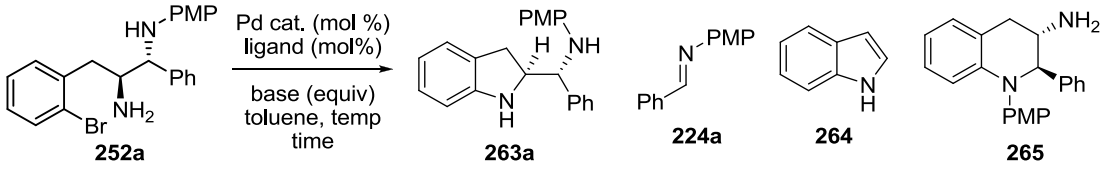
Scheme 101: Intramolecular *N*-arylations for the synthesis of polyazamacrocycles.

The use of this *N*-arylation chemistry in our system would demonstrate its first application to the synthesis of small ring fused heterocycles using substrates containing multiple reactive amine groups. The following sections detail our initial studies into the application of Pd-catalysed *N*-arylations to the synthesis of 2-aminomethylene indolines and 3-aminotetrahydroquinolines.

2.4.1 Indoline Synthesis

Our initial investigations into the intramolecular *N*-arylations focussed on the reaction of mono-protected diamine **252a**, the results of which are shown in Table 3. We began by applying the catalyst system that was developed by Buchwald *et al.* for the formation of simple indoline and tetrahydroquinoline structures.[142a] This first attempt was very promising as a 54% yield of indoline **263a** was obtained by heating diamine **252a** with $Pd(PPh_3)_4$, NaO*t*Bu and K_2CO_3 in toluene at 90 °C for 3 h (Table 3, entry 1). The product was accompanied by trace amounts of imine **224a** and indole (**264**), formed due to the slight instability of **263a** to oxidative cleavage under the reaction conditions. Rigorous drying of the bases, degassing of the solvent and performing the reaction at 100 °C gratifyingly increased the yield of indoline **263a** to 91% (Table 3, entry 2). Although a satisfactory yield had already been obtained, various other catalyst systems were also investigated. The use of $Pd_2(dba)_3$, P(*o*-tol)$_3$ and $CsCO_3$, conditions previously employed by the groups of Jackson and Buchwald for the synthesis of 2-substituted indolines,[142b,c]

gave poor conversion to the desired product (Table 3, entry 3). The use of Pd(dppf)Cl_2/dppf and $Pd_2(dba)_3$/BINAP catalyst systems gave moderate to good yields of indoline **263a** (Table 3, entries 3 and 4). These conditions, interestingly, also gave small amounts of tetrahydroquinoline **265**. It was found that the $Pd(PPh_3)_4$-catalysed cyclisation could also be performed with only NaO*t*Bu as a base, however, the reaction did not proceed as cleanly as those performed with two bases resulting in a lower yield of 77% (Table 3, entry 8). This is in agreement with observations made by Buchwald *et al.*[142a] Using only the weaker base K_2CO_3 reduced the rate of reaction and resulted in increased conversion to tetrahydroquinoline **265** (Table 3, entry 10).



Entry	Catalyst (mol%) Ligand (mol%)	Base (equiv)	T/°C (time/h)	Conversion (%)[a]		
				263a	224a+264	265
1	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (1.6) K_2CO_3 (1.6)	90 (4)	94 (54)	6	0
2[b]	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (1.6) K_2CO_3 (1.6)	100 (4)	>95 (91)	<5	0
3	$Pd_2(dba)_3$ (3.3) P(*o*-tol)$_3$ (13.3)	$CsCO_3$ (4.0)	100 (27)	21	<5	0
4	Pd(dppf)Cl_2 (5.0) dppf (15)	NaO*t*Bu (1.6)	100 (5)	70 (65)	<5	5
5	$Pd_2(dba)_3$ (5.0) BINAP (15)	NaO*t*Bu (1.6)	100 (5)	73 (51)	6	9
6	$Pd(OAc)_2$ (5.0) P(*o*-tol)$_3$ (15)	NaO*t*Bu (1.6)	100 (5)	27	5	0
7	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (1.6)	100 (5)	32	<5	0
8	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (2.5)	100 (18)	85 (77)	6	6
9	$Pd(PPh_3)_4$ (5.0)	K_2CO_3 (1.6)	100 (5)	24	0	<5
10	$Pd(PPh_3)_4$ (5.0)	K_2CO_3 (2.5)	100 (18)	69 (48)	0	17
11	$Pd(PPh_3)_4$ (5.0)	Cs_2CO_3 (1.6)	100 (5)	30	0	0

[a] Determined by ^{1}H NMR. Numbers in parenthesis show purified yield. [b] Reaction performed with rigorously dried bases and degassed solvent.

Table 3: Optimisation of indoline formation.

The mechanism of this intramolecular *N*-arylation is likely to be similar to that proposed by Rouden *et al.* (see Scheme 100).[143g] After oxidative addition of the palladium catalyst to the Ar–Br bond to form complex **266**, initial coordination of the primary amine to form complex **267** occurs selectively (Figure 20). This selectivity arises from the kinetically favoured formation of the six-membered ring over the seven-membered ring, and also the lower steric constraints caused by the primary amine compared to the secondary amine. Furthermore, the lower nucleophilicity of the PMP-protected amine would also disfavour formation of the seven-membered ring complex **268**. Once complex **267** is formed, equilibration to seven-membered ring complex **268** can occur. When a strong base, such as NaO*t*Bu, is used the formation of Pd-amido complex **269**, which can then undergo reductive elimination to form indoline **263a**, is faster than the equilibration to form complex **268**. This effect caused by the use of strong bases can explain the high selectivity for indoline formation observed when using NaO*t*Bu (>90:10 ratio of **263a**:**265**, see Table 3, entry 8). The increased formation of tetrahydroquinoline **265** when using a weaker base (80:10 ratio of **263a**:**265**, see Table 3, entry 10), such as K_2CO_3, could arise from a slower rate of formation of Pd-amido complex **269**. Equilibration to the seven-membered ring complex **268** then becomes competitive. Formation of Pd-amido complex **270** and reductive elimination to form tetrahydroquinoline **265** then becomes favourable so as to minimise the steric influence of the secondary amine at the palladium centre.

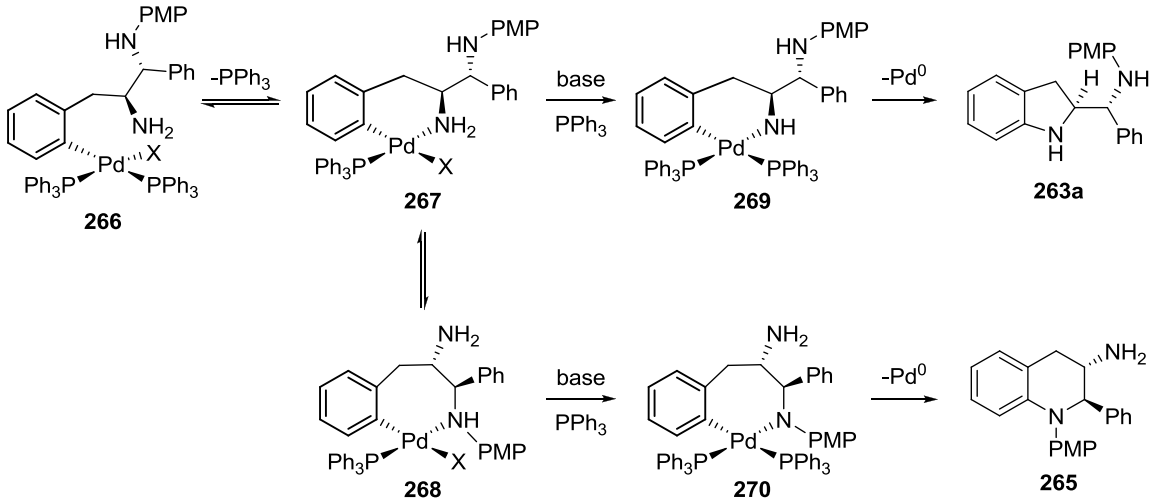
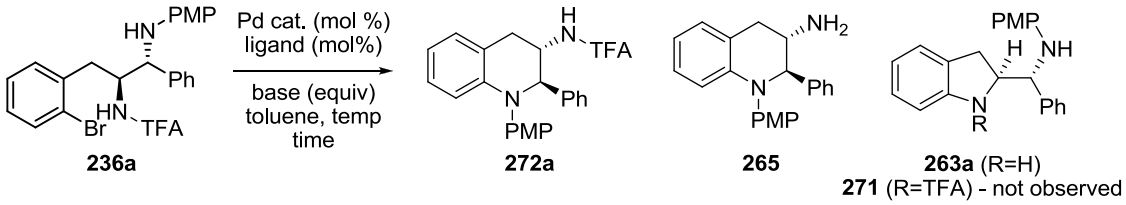


Figure 20: Proposed intramolecular *N*-arylation mechanism.

2.4.2 Tetrahydroquinoline Synthesis

Although small amounts of the tetrahydroquinoline **265** were formed in several reactions using mono-protected diamine **252a** (Table 3, entries 4, 5 and 8-10) further attempts to improve the selectivity for tetrahydroquinoline formation were unsuccessful. This is due to the significant difference in rates of formation of the five- and six-membered rings. Attention was therefore shifted to the cyclisation of orthogonally protected diamine **236a**, as it was postulated that the presence of the TFA protecting group would enable selective tetrahydroquinoline formation due to the significantly lower nucleophilicity of the TFA-protected nitrogen. The results of these investigations are shown in Table 4.

Initial attempts focussed on using the same conditions that had proved successful for the formation of indoline **263a**. Gratifyingly, complete reversal of selectivity was observed with no formation of TFA-protected indoline **271** detected (Table 4, entry 1). Tetrahydroquinoline **272a** was formed in 54% yield, along with small amounts of deprotected tetrahydroquinoline **265** and indoline **263a**. The longer reaction time of 18 h required for tetrahydroquinoline formation, due to the slower formation of a seven-membered ring palladacycle (*c.f.* complex **268** in Figure 20), allows unwanted side reactions to become competitive. These additional products are presumably formed *via* removal of the TFA group by *tert*-butoxide anions or hydroxide impurities present in the reaction. Deprotection prior to cyclisation results in the formation of mono-protected diamine **252a**, which can then undergo cyclisation forming indoline **263a**, whereas deprotection after cyclisation leads to tetrahydroquinoline **265**. Various other catalyst systems were investigated but all failed to compete with the $Pd(PPh_3)_4$ catalysed reaction (Table 4, entries 2 and 3). By varying the bases used in the reaction it became clear that the TFA group would not tolerate NaO*t*Bu, with deprotection occurring both before and after cyclisation to give multiple products (Table 4, entry 4). Using only K_2CO_3 gave a very clean reaction affording 76% of **272a** (Table 4, entry 5). This high yield obtained when using K_2CO_3 is in agreement with the previous observation that the use of only K_2CO_3 as the base in the reaction of mono-protected diamine **252a** leads to increased levels of tetrahydroquinoline **265** formation (see Table 3, entry 10). Increasing the equivalents of K_2CO_3 and increasing the temperature to 100 °C resulted in complete conversion to tetrahydroquinoline **272a**, which was isolated in 98% yield (Table 4, entry 7).



236a **272a** **265** **263a** (R=H)
271 (R=TFA) - not observed

Entry	Catalyst (mol%)	Base (equiv)	T/°C (time/h)	Conversion (%)[a]		
				272a	265	263a
1	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (1.6), K_2CO_3 (1.6),	90 (18)	72 (54)	10	12 (7)
2	$Pd(dppf)Cl_2$ (5.0), dppf (15)	NaO*t*Bu (1.4)	90 (18)	20	0	5
3	$Pd_2(dba)_3$ (2.5), BINAP (7.5)	NaO*t*Bu (1.4)	90 (5)	<5	0	<5
4	$Pd(PPh_3)_4$ (5.0)	NaO*t*Bu (1.6)	90 (18)	71 (54)	19	<5
5	$Pd(PPh_3)_4$ (5.0)	K_2CO_3 (1.6)	90 (18)	90 (76)	0	0
6	$Pd(PPh_3)_4$ (5.0)	LiHMDS (1.6)	90 (18)	<10	0	0
7	$Pd(PPh_3)_4$ (5.0)	K_2CO_3 (2.5)	100 (18)	100 (98)	0	0

[a] Determined by ^{1}H NMR. Numbers in parenthesis show purified yield.

Table 4: Optimisation of tetrahydroquinoline formation.

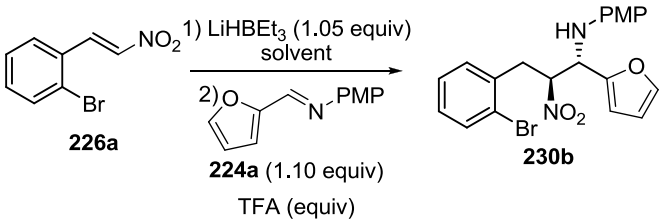
Following the successful synthesis of both indoline **263a** and tetrahydroquinoline **272a**, in high yield and with excellent levels of diastereoselectivity, attention was then turned to investigating the scope of the synthesis.

2.5 Substrate Scope

To demonstrate the robustness of our synthesis of fused heterocycles we needed to investigate the substrate scope. This involved the use of a variety of different nitroalkene and imine starting materials. The results of these investigations are described in the following chapter.

2.5.1 Nitro-Mannich Reaction

The investigations into the scope of the heterocycle synthesis began with the reductive nitro-Mannich reaction. Initial reactions, using the conditions described previously (see Scheme 93, Section 2.2.3), with a variety of different imines revealed that using electron rich heteroaryl substituted imines, such as 2-furyl imine **224b**, resulted in no or very poor diastereoselectivity. Optimisation studies were therefore performed with the aim of improving selectivity. The original conditions that proved to be very successful with phenyl imine **224a** resulted in no selectivity, giving a 1:1 ratio of *anti*- and *syn*-diastereomers (Table 5, entry 1). It was postulated that under these conditions the reaction rate with electron rich imines was too high and led to a non-selective reaction, so by using a weaker acid to reduce the reaction rate the selectivity may be improved. Indeed, when AcOH was used an improved *anti*:*syn* ratio of 65:35 was obtained but with a lower conversion of only 77% (Table 5, entry 2). It was found that by lowering the equivalents of TFA used in the reaction the diastereoselectivity was improved to a similar level to that obtained with AcOH but without the drop in conversion (Table 5, entry 3). Lowering the amount of AcOH, however, resulted in no reaction (Table 5, entry 4). Changing to non-coordinating solvents further increased the diastereoselectivity with the use of dichloromethane providing *β*-nitroamine **230b** in excellent conversion and high selectivity for the *anti*-diastereomer (Table 5, entries 5-7). This solvent effect is presumably due to the more Lewis basic solvents disrupting the hydrogen-bonded ordered chair-like TS. The use of trichloroacetic acid (TCA) gave similar levels of selectivity (Table 5, entry 8). It was found that a slight increase in selectivity could be obtained by using an excess of imine compared to TFA (Table 5, entry 9). However, it was later found that the presence of excess imine in the nitro-Mannich reaction complicated the purification of the products after TFA protection so 1.10 equiv. of imine was used in the standard conditions.



Entry	Solvent	Acid (equiv)	Conv. (%)[a]	*anti*:*syn*[a]
1	THF	TFA (2.50)	>95	50:50
2	THF	AcOH (2.50)	77	65:35
3	THF	TFA (1.15)	>95	65:35
4	THF	AcOH (1.15)	0	-
5	Et_2O	TFA (1.15)	>95	80:20
6	toluene	TFA (1.15)	>95	80:20
7	CH_2Cl_2	TFA (1.15)	>95	85:15
8	CH_2Cl_2	TCA (1.15)	>95	85:15
9[b]	CH_2Cl_2	TFA (1.15)	>95	90:10

[a] Determined by ^{1}H NMR. [b] reaction performed with 1.50 equiv. imine **224b**.

Table 5: Optimisation of the nitro-Mannich reaction.

One possible explanation for the lower selectivity obtained with excess TFA is that protonation of both the imine nitrogen, forming iminium species **273**, and the nitronate, forming nitronic acid **274**, occurs resulting in a faster reaction (Figure 21). When only a single equiv. of TFA is used an equilibrium between **273** and **274** exists. This reduces the rate of reaction and leads to a favourable formation of chair-like TS **275** and results in high selectivity for the *anti*-diastereomer. Whereas, with excess TFA the reaction rate is increased leading to competing reactions *via* chair-like TS **276** and open TS **277**. The slower formation of TS **276**, compared to TS **275** when a single equiv. of TFA is used, allows the reaction to also proceed through the open TS **277** resulting in a less selective reaction. The drastic difference in selectivity between phenyl-imine **224a** and furyl-imine **224b** could be accounted for by the higher basicity of the imine nitrogen in the electron rich furyl-imine **224b**. The result is a faster rate of reaction which can proceed unselectively through both TS **276** and TS **277**. The high selectivity achieved in the reaction with phenyl-imine **224a**, even when an excess of acid is used, results from the slower rate of

reaction. This allows effective formation of TS **276**, therefore minimising the amount of reaction that proceeds through open TS **277**. It is also possible that the greater stability of the furyl iminium species **273** facilitates retro-addition, thereby leading to a more thermodynamically controlled reversible reaction.

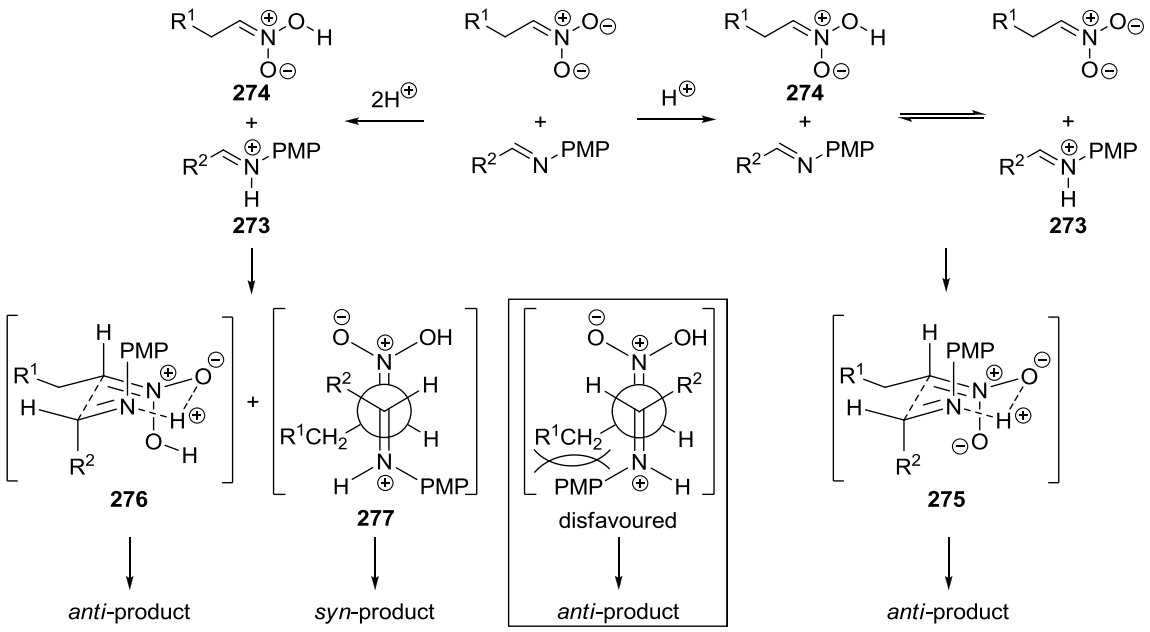
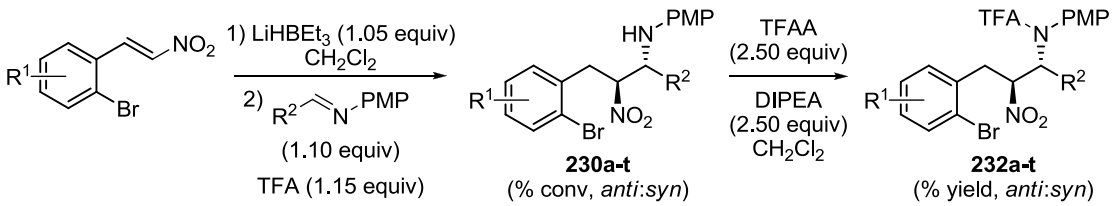
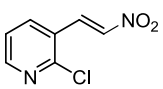


Figure 21: Origin of diastereoselectivity.

The optimised reductive nitro-Mannich conditions were then applied to a range of nitrostyrenes and imines (Table 6). The reactions proceeded with excellent diastereoselectivity and good yields of the *β*-nitroacetamide products **232** for a wide range of imines, including those derived from aryl, heteroaryl and alkyl substituents (Table 6, entries 1-5 and 8-15). The imines derived from cyclohexyl and *tert*-butyl aldehydes performed well in the nitro-Mannich reaction, with good conversion and diastereoselectivity obtained, but the product *β*-nitroamines **230f** and **230g** failed to undergo TFA protection, presumably due to the steric influence of these bulky alkyl groups preventing reaction (Table 6, entries 6 and 7). The 2-trifluoromethylphenyl analogue **230m** also suffered from a slower rate in the TFA protection and required the use of additional TFAA and base to achieve satisfactory yields of **232m** (Table 6, entry 13). A number of substituted 2-bromo-*β*-nitrostyrenes were also employed in the reaction and gave uniformly high yields and diastereoselectivities (Table 6, entries 16-19). The use of the nitroalkene derived from 2-chloropyridine-3-carboxaldehyde also performed well, giving *β*-nitroacetamide **232t** in good yield and high diastereoselectivity (Table 6, entry 20).



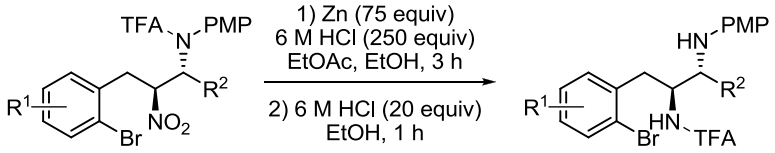
Entry	R^1	R^2	*β*-Nitroamine 230 (conv., *anti*:*syn*)[a]	*β*-Nitroacetamide 232 (yield, *anti*:*syn*)[b]
1	H	Ph	**230a** (>95%, >95:5)	**232a** (71%, >95:5)
2	H	2-furyl	**230b** (>95%, 85:15)	**232b** (70%, >95:5)
3	H	3-furyl	**230c** (>95%, 85:15)	**232c** (69%, >95:5)
4	H	2-thiophenyl	**230d** (>95%, 90:10)	**232d** (74%, >95:5)
5	H	*n*-pentyl	**230e** (>95%, 95:5)	**232e** (85%, >95:5)
6	H	cyclohexyl	**230f** (>95%, 80:20)	**232f** (no reaction)
7	H	*tert*-butyl	**230g** (90%, 85:15)	**232g** (no reaction)
8	H	2-Me-C_6H_4	**230h** (>95%, 90:10)	**232h** (81%, >95:5)
9	H	2-Br-C_6H_4	**230i** (>95%, 90:10)	**232i** (83%, >95:5)
10	H	2-MeO-C_6H_4	**230j** (>95%, 90:10)	**232j** (83%, >95:5)
11	H	3-MeO-C_6H_4	**230k** (>95%, >95:5)	**232k** (83%, >95:5)
12	H	4-MeO-C_6H_4	**230l** (95%, >95:5)	**232l** (82%, >95:5)
13	H	2-CF_3-C_6H_4	**230m** (>95%, 90:10)	**232m** (60%, >95:5)[c]
14	H	3-CF_3-C_6H_4	**230n** (>95%, >95:5)	**232n** (91%, >95:5)
15	H	4-CF_3-C_6H_4	**230o** (>95%, >95:5)	**232o** (90%, >95:5)
16	5-F	Ph	**230p** (>95%, >95:5)	**232p** (82%, >95:5)
17	4-MeO,5-MeO	Ph	**230q** (>95%, >95:5)	**232q** (88%, >95:5)
18	4-MeO,5-MeO	2-MeO-C_6H_4	**230r** (>95%, 85:15)	**232r** (72%, >95:5)
19	3-OBn,4-MeO	Ph	**230s** (>95%, >95:5)	**232s** (82%, >95:5)
20		Ph	**230t** (>95%, >95:5)	**232t** (59%, >95:5)

[a] Determined by ^{1}H NMR. [b] Isolated yields. [c] Protection performed with 5.0 equiv. TFAA and 5.0 equiv. pyridine.

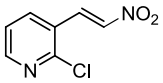
Table 6: Scope of the nitro-Mannich reaction.

2.5.2 Nitro Reduction

The successfully synthesised *β*-nitroacetamides **232a-e** and **232h-t** were then used to investigate the scope of the nitro reduction (Table 7). The reduction gave uniformly high yields in the majority of cases with yields ranging from 79% to 95% (Table 7, entries 1-6 and 8-15). Problems arising from debromination occurred when forming compounds **236i**, **236r** and **236s** (Table 7, entries 7, 16 and 17). Although trace amounts of the respective debrominated products were formed with the majority of analogues, these could be removed either by column chromatography or recrystallisation. The reductions to form compounds **236i**, **236r** and **236s**, however, resulted in significant amounts of debrominated product which could not be removed by either column chromatography or recrystallisation, which prevented the isolation of these products in pure form. It should be noted that debromination of **236i** occurred at the C–Br bond in the R^2 substituent, resulting in the formation of **236a**. The reactive C–Cl bond in pyridine analogue **232t** was not stable under the reduction conditions and complete dechlorination resulted (Table 7, entry 18).



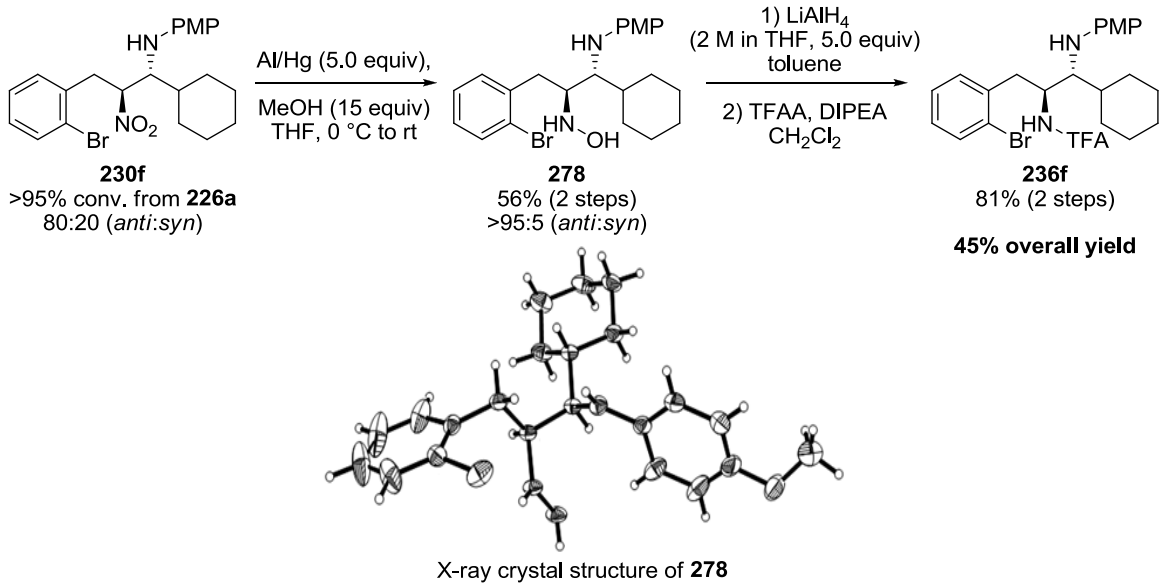
Entry	R^1	R^2	Product	Yield (%)[a]
1	H	Ph	**236a**	89
2	H	2-furyl	**236b**	91
3	H	3-furyl	**236c**	93
4	H	2-thiophenyl	**236d**	82
5	H	*n*-pentyl	**236e**	95
6	H	2-Me-C_6H_4	**236h**	91
7	H	2-Br-C_6H_4	**236i**	75% conv. (25%)[b,c]
8	H	2-MeO-C_6H_4	**236j**	94
9	H	3-MeO-C_6H_4	**236k**	82
10	H	4-MeO-C_6H_4	**236l**	91

11	H	2-CF_3-C_6H_4	**236m**	82
12	H	3-CF_3-C_6H_4	**236n**	88
13	H	4-CF_3-C_6H_4	**236o**	88
14	5-F	Ph	**236p**	89
15	4-MeO,5-MeO	Ph	**236q**	79
16	4-MeO,5-MeO	2-MeO-C_6H_4	**236r**	90% conv. (10%)[b,c]
17	3-OBn,4-MeO	Ph	**236s**	65% conv. (35%)[b,c]
18		Ph	**236t**	0% conv. (>95%)[b]

[a] Isolated yields. [b] Number in parenthesis shows conversion to dehalogenated *β*-aminoacetamide. Conversions determined by ^{1}H MNR. [c] Debromination caused inseparable mixture of products.

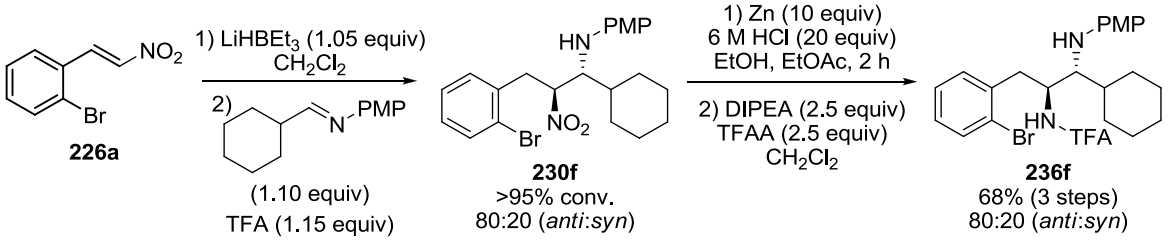
Table 7: Scope of the nitro reduction.

To overcome the difficulties encountered in forming compounds **236i**, **236r**, **236s** and **236t**, which could not be formed cleanly by reduction of their respective *β*-nitroacetamide **232**; and to form the desired reduction products from *β*-nitroamines **230f** and **230g**, which failed to undergo TFA protection, alternative routes to the orthogonally protected diamines were investigated. The use of the Al/Hg reduction protocol described in Scheme 96 (Section 2.3.2) was implemented and initially applied to the reduction of cyclohexyl analogue **230f** (Scheme 102). Using the previously described conditions, the reduction proceeded smoothly to yield *β*-aminohydroxylamine **278** which was isolated in 56% yield and with excellent dr after separation of the diastereomers by column chromatography. The *anti*-conformation of **278** was confirmed by single-crystal X-ray crystallography. The use of the previously described $LiAlH_4$ reduction conditions (solid $LiAlH_4$ in Et_2O) to promote the reduction of hydroxylamine **278** was found to result in significant amounts of degradation and poor yields. Much cleaner reactions could be achieved by using $LiAlH_4$ as a 2M solution in THF and performing the reaction in toluene. Subsequent treatment of crude diamine **252f** with TFAA and DIPEA allowed the formation of orthogonally protected diamine **236f** in 81% yield over the two steps.



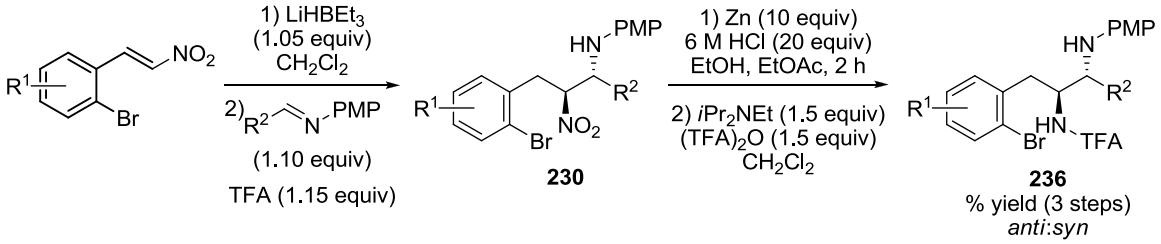
Scheme 102: Al/Hg reduction strategy.

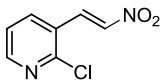
The use of the Zn/HCl reduction on crude β-nitroamines **230** was also investigated. It was previously thought that these compounds would not be stable under the acidic reduction conditions due to their propensity to undergo retro-addition. However, in the absence of a TFA-protecting group the reduction becomes much more facile and can be performed with only 20 equiv. of HCl and 10 equiv. of zinc. The increased rate of reduction minimises the amount of retro-addition that occurs. These conditions were used to reduce β-nitroamine **230f** which, after subsequent TFA protection of crude diamine **252f**, gave a 68% yield of orthogonally protected diamine **236f** (Scheme 103). It was found that separation of the diastereomers of **236f** could not be achieved effectively by column chromatography but recrystallisation could be used to obtain the major *anti*-diastereomer in >95:5 dr. The use of this Zn/HCl reduction was found to be preferable to the Al/Hg/$LiAlH_4$ protocol as it gave a higher overall yield (68% compared to 45%), required only a single chromatographic purification and also avoided the use of highly toxic mercury reagents.



Scheme 103: Alternative Zn/HCl reduction strategy.

These Zn/HCl reduction conditions were then applied to the remaining *β*-nitroamine analogues **230g**, **230i** and **230r-t** (Table 8). The reduction gave orthogonally protected 1,2-diamines **236g**, **236i**, **236r-s** in moderate to good yields and with no observed debromination (Table 8, entries 1-4). It was again found that separation of the diastereomers of the TFA-protected diamines **236** could not be achieved effectively by column chromatography but recrystallisation could be used to obtain the major *anti*-diastereomers in >95:5 dr, albeit in relatively poor yield. Due to the high reactivity of the C–Cl bond in pyridine analogue **230t** application of the Zn/HCl reduction protocol again resulted in dechlorination (Table 8, entry 5). This was also the case when the Al/Hg/$LiAlH_4$ reduction protocol was used, as the reduction of the hydroxylamine intermediate with $LiAlH_4$ resulted in dechlorination. The failure to synthesise diamine **236t** represents a limitation of the current synthesis and further investigations into milder reduction protocols are required. However, it was thought the use of diamines **236a-s** would be sufficient to demonstrate the scope of the heterocycle synthesis so further investigations into the reduction of *β*-nitroamine **230t** were not performed.



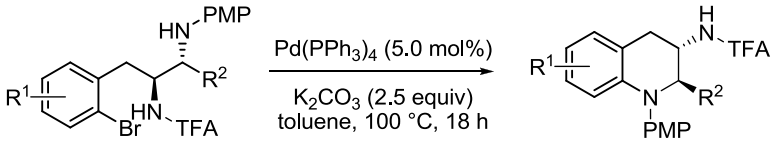
Entry	R^1	R^2	Product	Yield (%)[a]	Yield (%) after recryst.[a]
1	H	*tert*-butyl	**236g**	65 (85:15)	27 (>95:5)
2	H	2-Br-C_6H_4	**236i**	62 (95:5)	41 (>95:5)
3	4-MeO,5-MeO	2-MeO-C_6H_4	**236r**	40 (90:10)	14 (>95:5)
4	3-OBn,4-MeO	Ph	**236s**	43 (>95:5)	-[c]
5[b]		Ph	**236t**	0	-

[a] Isolated yields. Number in parenthesis shows *anti*:*syn* ratio. [b] Complete degradation observed. [c] No recrystallisation required.

Table 8: Scope of the Zn/HCl nitro reduction of *β*-nitroamines **230**.

2.5.3 Tetrahydroquinoline Synthesis

With the successful formation of *β*-aminoacetamides **236a-s** complete, the synthesis of the fused heterocyclic structures was carried out. The results of the investigation into the scope of the synthesis of tetrahydroquinolines **272** are shown in Table 9. As can be seen, the tetrahydroquinolines were formed in excellent yields in nearly all cases, including those analogues containing electron rich aryl bromides (Table 9, entries 17-18) Examples containing bulky alkyl substituents, such as cyclohexyl and *tert*-butyl analogues **272f** and **272g**, were formed in lower yields due to the unexpected formation of indolines **279** and **280** in 15% and 38% yield, respectively (see Table 9, entries 6 and 7, and Scheme 104). This unexpected indoline formation presumably arises from the steric influences of these large groups giving the intermediates a favourable conformation for indoline formation, such that they are able to overcome the lower reactivity of the amide nitrogen. The use of 10 mol% $Pd(PPh_3)_4$ was required to achieve a good yield of the cyclohexyl tetrahydroquinoline analogue **272f** due to the instability of **236f** under the reaction conditions (Scheme 104).



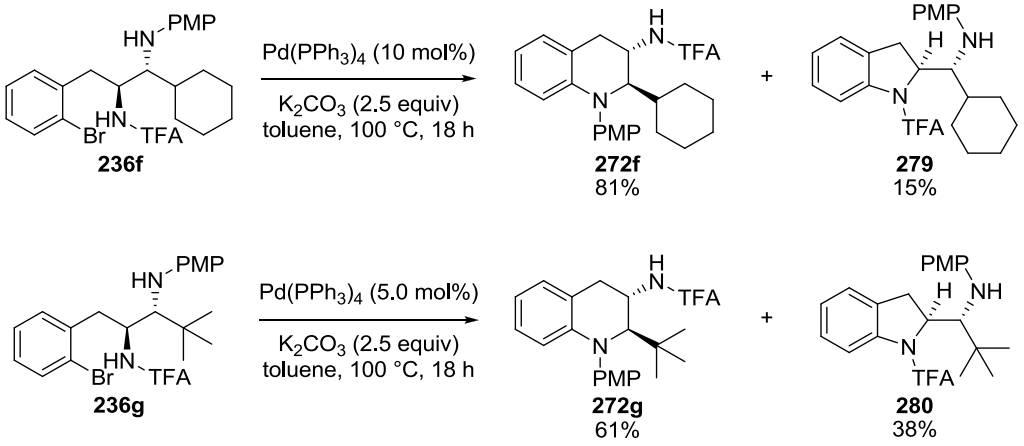
236a-s **272a-s** (% yield)

Entry	R^1	R^2	Product	Yield (%)[a]
1	H	Ph	**272a**	98
2	H	2-furyl	**272b**	92
3	H	3-furyl	**272c**	94
4	H	2-thiophenyl	**272d**	91
5	H	*n*-pentyl	**272e**	89
6	H	cyclohexyl	**272f**	81[b]
7	H	*tert*-butyl	**272g**	61
8	H	2-Me-C_6H_4	**272h**	88
9	H	2-Br-C_6H_4	**272i**	54[b] (27)[c]

10	H	2-MeO-C_6H_4	**272j**	98
11	H	3-MeO-C_6H_4	**272k**	90
12	H	4-MeO-C_6H_4	**272l**	98
13	H	2-CF_3-C_6H_4	**272m**	97
14	H	3-CF_3-C_6H_4	**272n**	99
15	H	4-CF_3-C_6H_4	**272o**	99
16	5-F	Ph	**272p**	93
17	4-MeO,5-MeO	Ph	**272q**	91
18	4-MeO,5-MeO	2-MeO-C_6H_4	**272r**	88
19	3-OBn,4-MeO	Ph	**272s**	31

[a] Isolated yields. [b] 10 mol% $Pd(PPh_3)_4$ used. [c] Number in parenthesis shows yield obtained when using 5 mol% $Pd(PPh_3)_4$.

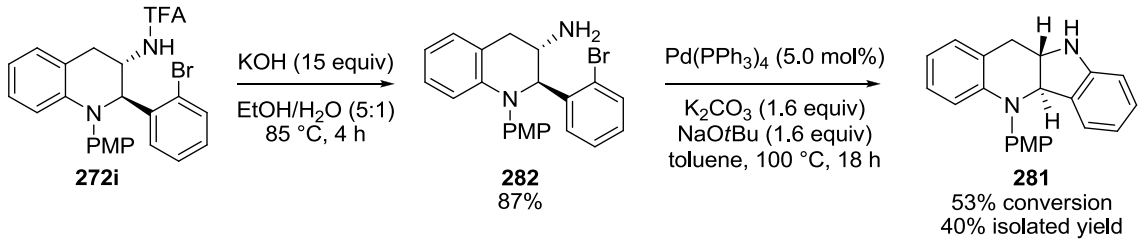
Table 9: Scope of the tetrahydroquinoline synthesis.



Scheme 104: TFA-protected indoline formation.

When dibromo diamine analogue **236i** was submitted to the cyclisation conditions tetrahydroquinoline **272i** was formed in only 27% yield due to competing oxidative addition of the palladium catalyst to both C–Br bonds (Table 9, entry 9). Although the yield was low, the reaction demonstrates surprisingly high selectivity (~85:15) for the desired C-Br bond considering this selectivity arises from relatively small steric differences between each C–Br bond. The yield of **272i** could be improved to 54% by doubling the amount of catalyst to 10 mol%. The cyclisation also failed to provide a satisfactory yield of tetrahydroquinoline **272s**, presumably due to the formation of a sterically crowded product with the PMP and OBn groups in close proximity to one another (Table 9, entry 19).

The aryl bromide containing tetrahydroquinoline **272i** was then used to synthesise tetracycle **281**, first by removal of the TFA group, furnishing primary amine **282** in 87% yield, and subsequent cyclisation, which proceeded in 40% yield (Scheme 105). The low yield of the cyclisation reaction is believed to be due to the formation of a relatively strained ring system. The *trans* configuration of **281** was confirmed by the large coupling constant (J = 11.5 Hz) between the vicinal C–H groups in the ^{1}H NMR.



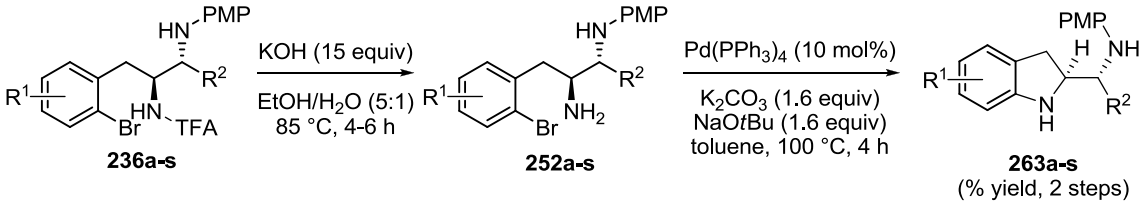
Scheme 105: Synthesis of tetracycle **282**.

2.5.4 Indoline Synthesis

The final set of fused heterocycles to be synthesised were the 2-aminomethylene indolines **263a-s**. Although the original conditions developed for the synthesis of indoline **263a** from diamine **252a** used 5 mol% of $Pd(PPh_3)_4$, it was found that the by-products resulting from the instability of some of the indoline products caused a decrease in catalyst efficiency and that more reproducible results could be obtained by increasing the amount of $Pd(PPh_3)_4$ to 10 mol%. This catalyst loading was then used in the investigation of the scope of indoline formation. The synthesis of indolines **263a-s** required initial removal of the TFA protecting group from the orthogonally protected diamines **236a-s** followed by cyclisation of the resulting mono-protected diamines **252a-s**. The results of the investigation are shown in Table 10.

The removal of the TFA protecting group was achieved in excellent yield for all the analogues investigated, providing mono-protected diamines **252a-s** (Table 10, entries 1-19). The cyclisation reactions proceeded with moderate to high yield to furnish indoline products **263a-s**. The yields were consistent for a range of aryl, heteroaryl and alkyl containing analogues (Table 10, entries 1-15). The higher yields obtained for the cyclohexyl and *tert*-butyl analogues **263f** and **263g** (Table 10, entries 6 and 7) support the hypothesis that these bulky groups provide the cyclisation intermediates with a favourable

conformation for indoline formation (*c.f.* the formation of TFA-protected indolines **279** and **280**, Scheme 104). The yields of the substituted indolines **263p-s** were found to be lower as a result of their lower stabilities, which resulted in difficult purifications.

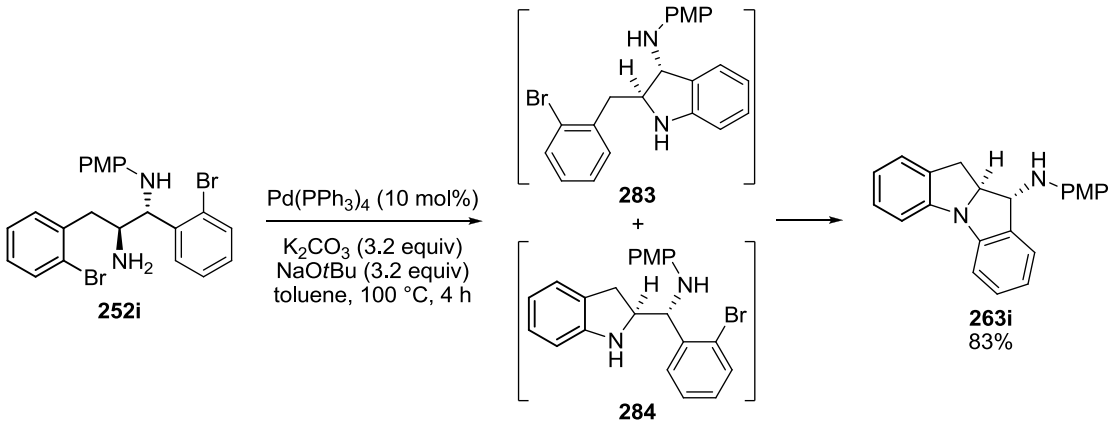


Entry	R^1	R^2	Diamine 252 (% yield)[a]	Indoline 263 (% yield)[a]
1	H	Ph	**252a** (94)	**263a** (91)[b]
2	H	2-furyl	**252b** (92)	**263b** (75)
3	H	3-furyl	**252c** (96)	**263c** (69)
4	H	2-thiophenyl	**252d** (93)	**263d** (79)
5	H	*n*-pentyl	**252e** (96)	**263e** (69)
6	H	cyclohexyl	**252f** (98)	**263f** (82)
7	H	*tert*-butyl	**252g** (100)	**263g** (87)
8	H	2-Me-C_6H_4	**252h** (96)	**263h** (77)
9	H	2-Br-C_6H_4	**252i** (100)	**263i** (83)[c]
10	H	2-MeO-C_6H_4	**252j** (85)	**263j** (66)
11	H	3-MeO-C_6H_4	**252k** (96)	**263k** (69)
12	H	4-MeO-C_6H_4	**252l** (100)	**263l** (64)
13	H	2-CF_3-C_6H_4	**252m** (88)	**263m** (74)
14	H	3-CF_3-C_6H_4	**252n** (100)	**263n** (59)
15	H	4-CF_3-C_6H_4	**252o** (98)	**263o** (80)
16	5-F	Ph	**252p** (100)	**263p** (50)
17	4-MeO,5-MeO	Ph	**252q** (95)	**263q** (50)
18	4-MeO,5-MeO	2-MeO-C_6H_4	**252r** (94)	**263r** (45)
19	3-OBn,4-MeO	Ph	**252s** (88)	**263s** (66)

[a] Isolated yields. [b] 5 mol% $Pd(PPh_3)_4$ was used. [c] 3.2 equiv. NaO*t*Bu and 3.2 equiv. K_2CO_3 was used.

Table 10: Scope of the indoline synthesis.

The product formed from the cyclisation of dibromo diamine **252i** was tetracycle **263i**, resulting from a double cyclisation process (Table 10, entry 9). When the standard set of conditions were used a mixture of products was obtained that comprised of **263i** and the two mono-arylated products **283** and **284** (Scheme 106). The use of 3.2 equiv. of both NaO*t*Bu and K_2CO_3 was required for complete conversion to tetracycle **263i**.



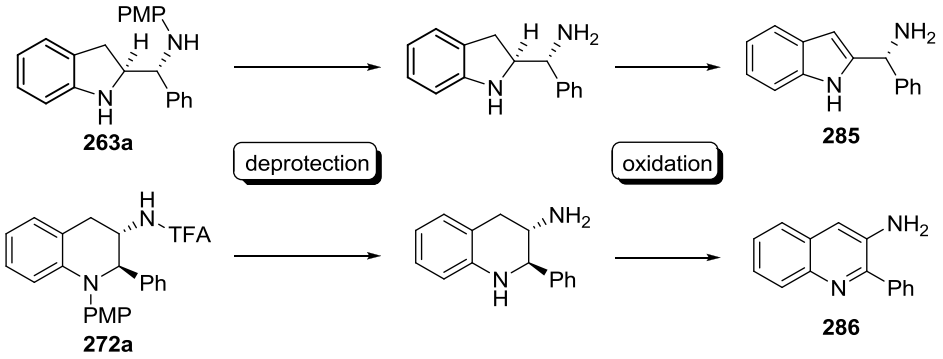
Scheme 106: Synthesis of tetracycle **263i**.

The yields for the formation of indolines **263a-s** were generally found to be lower than those obtained for the formation of tetrahydroquinolines **272a-s**. This is due to the lower stability of the indoline products, some of which proved to be difficult to purify due to degradation during column chromatography. This was particularly evident for the substituted indolines **263p-r** which could only be isolated in relatively poor yields (Table 10, entries 16-18).

The successful synthesis of the fused heterocyclic products, including 2-aminomethylene indolines **263a-s** and 3-amino-tetrahydroquinolines **272a-s**, has demonstrated the broad substrate scope of this methodology. The following chapter describes some studies that were performed to enable further functionalisation of these fused heterocyclic products.

2.6 Further Derivatisation

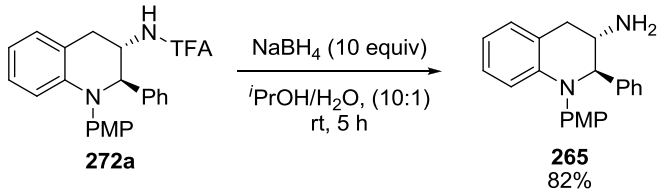
The presence of the 1,2-diamine moiety in the fused heterocyclic products **263a-s** and **272a-s** provides the opportunity for further functionalisation of these structures. The initial aim was to attempt to remove the PMP and TFA protecting groups and also to investigate the oxidation of the heterocycles to form indole **285** and quinoline **286** (Scheme 107). Although this aromatisation process would lead to the destruction of the two vicinal stereocentres it would still be a useful transformation due to the importance of the indole and quinoline motifs.



Scheme 107: Proposed deprotection and aromatisation of indoline **263a** and tetrahydroquinoline **272a**.

2.6.1 TFA Deprotection

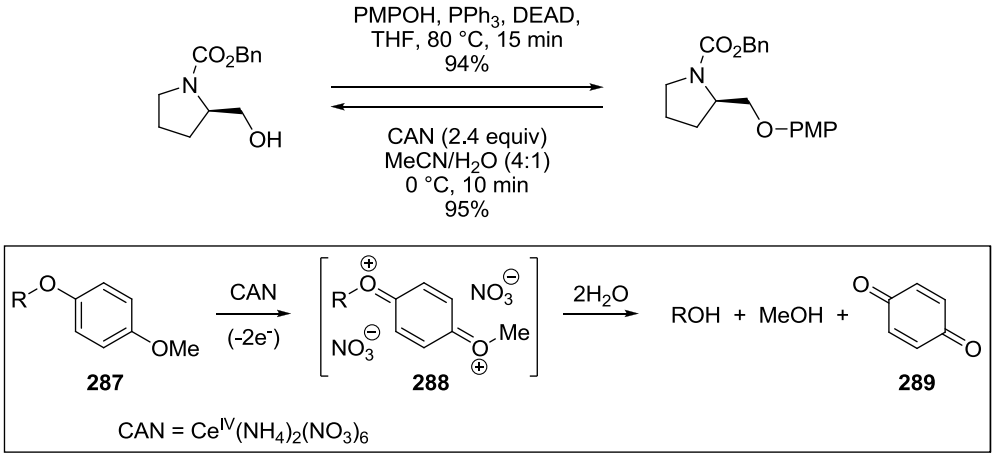
Removal of the TFA group in tetrahydroquinoline **272a** proved to be straightforward. This had previously been demonstrated on tetrahydroquinoline **272i** using the KOH deprotection method, forming primary amine **281** in 87% yield (see Scheme 105). In the absence of an aryl bromide the reaction could also be performed under milder conditions by using $NaBH_4$ to generate primary amine **265** in 82% (Scheme 108).



Scheme 108: TFA deprotection of tetrahydroquinoline **272a**.

2.6.2 PMP Deprotection

The PMP protecting group was originally introduced by Fukuyama *et al.* in 1985 for the protection of alcohols.[145] It is an effective protecting group as it is stable to acidic, basic and reducing conditions but can be removed under mild oxidative conditions by treatment with CAN (Scheme 109). The deprotection involves a single electron transfer mechanism that requires the loss of two electrons from PMP-ether **287** to form the benzoquinone dication **288**. Hydrolysis of the oxocarbenium ions liberates the two free alcohols and 1,4-benzoquinone (**289**). The PMP protecting group has since been successfully applied as a useful amine protecting group as it can be removed under similar mild conditions by treatment with CAN or various other oxidants.[51,146]

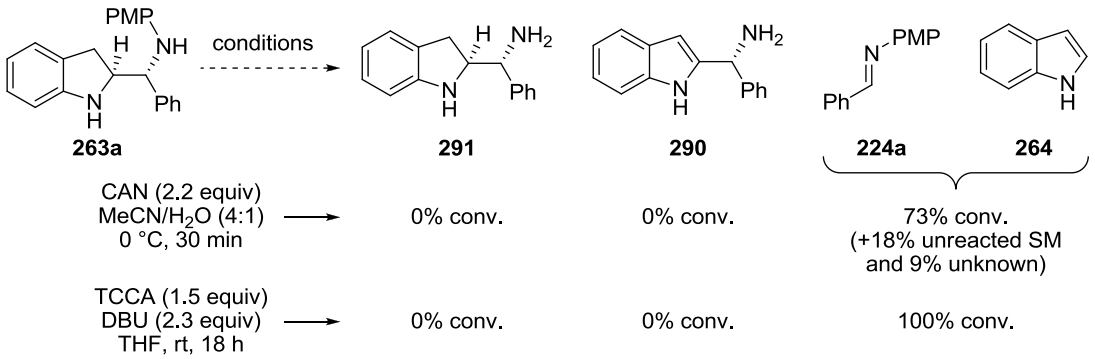


Scheme 109: The use of PMP for the protection of alcohols.

As the PMP deprotection involves the use of oxidants that are typically also used for the oxidation/aromatisation of heterocycles it was thought that the PMP-deprotection and aromatisation could be achieved in a single step. However, due to the similar conditions employed, selective removal of the PMP group while avoiding oxidation of the heterocycle may prove to be a challenge.

Investigations into the removal of the PMP group from indoline **263a** and oxidation to indole **290** proved to be unsuccessful due to the propensity of the indoline to undergo oxidative cleavage. Removal of the PMP group to form indoline **291** was attempted using the CAN conditions previously described by Anderson *et al.*[51] This led to 73% conversion to the oxidative cleavage products imine **224a** and indole (**264**), with 18% unreacted indoline **263a,** and 9% conversion to an unidentified product that was not indoline **291** or

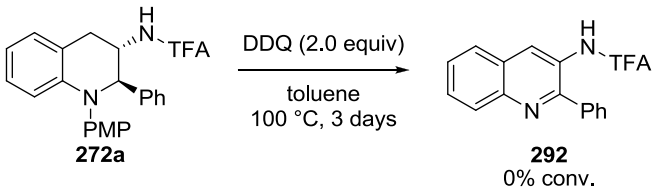
indole **290** (Scheme 110). Oxidation with trichloroisocyanuric acid (TCCA), a method used by Tilstam *et al.* for the aromatisation of indolines was also attempted.[147] This, however, led to complete degradation, again forming imine **224a** and indole (**264**) as the major products (Scheme 110).



Scheme 110: Attempted PMP deprotection of indoline **263a**.

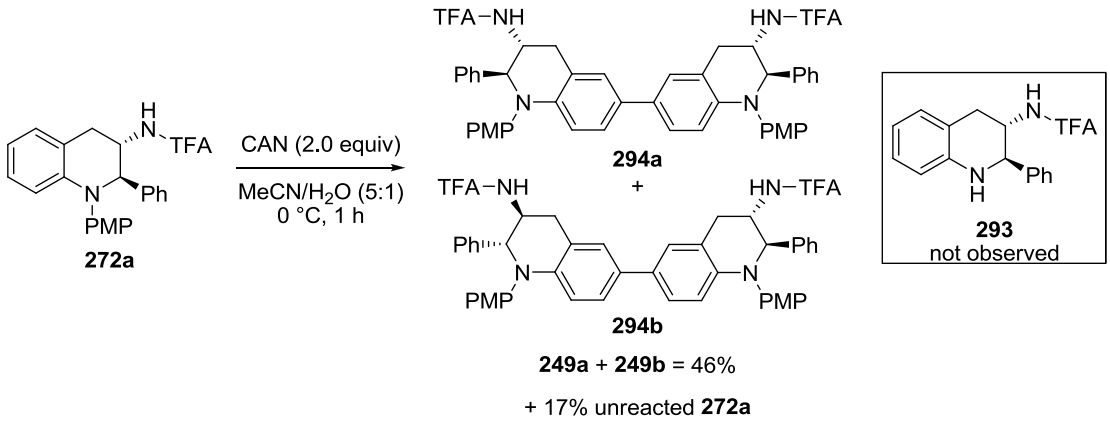
Due to the ease in which indoline **263a** underwent oxidative cleavage, and the failure to form any of the desired PMP-deprotection or aromatisation products, all subsequent efforts were focussed on the deprotection and/or aromatisation of tetrahydroquinoline **272a**, as it was hoped that this would be a more forgiving substrate.

Deprotection and aromatisation studies were performed on tetrahydroquinoline **272a** using a variety of methods. Aromatisation of **272a** with DDQ was attempted using conditions previously described by Cakmak *et al.* for the aromatisation of tetrahydroquinolines.[148] These conditions failed to give any of the desired aromatised product **292**, instead giving complete recovery of the starting material (Scheme 111). The oxidations performed by Cakmak *et al.* all involved tetrahydroquinolines without protection on the nitrogen. The presence of the PMP in tetrahydroquinoline **272a** is likely to be preventing effective oxidation with DDQ.



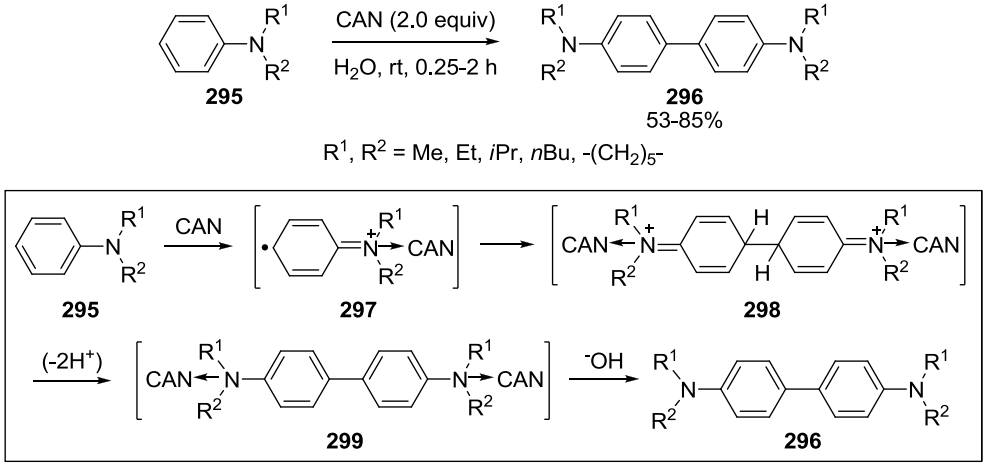
Scheme 111: Attempted aromatisation of tetrahydroquinoline **272a** with DDQ.

The use of CAN to affect the PMP deprotection of tetrahydroquinoline **272a** was also attempted by using the same conditions that were applied to indoline **263a** (see Scheme 110). Although no PMP deprotection product **293** was formed during the reaction, an oxidative dimerisation of **272a** occurred to yield bis-tetrahydroquinoline **294** in 46% yield as a mixture of *meso* (**294a**) and C_2 symmetric (**294b**) products (approximately 1:1 ratio determined by ^{13}C NMR) (Scheme 112).



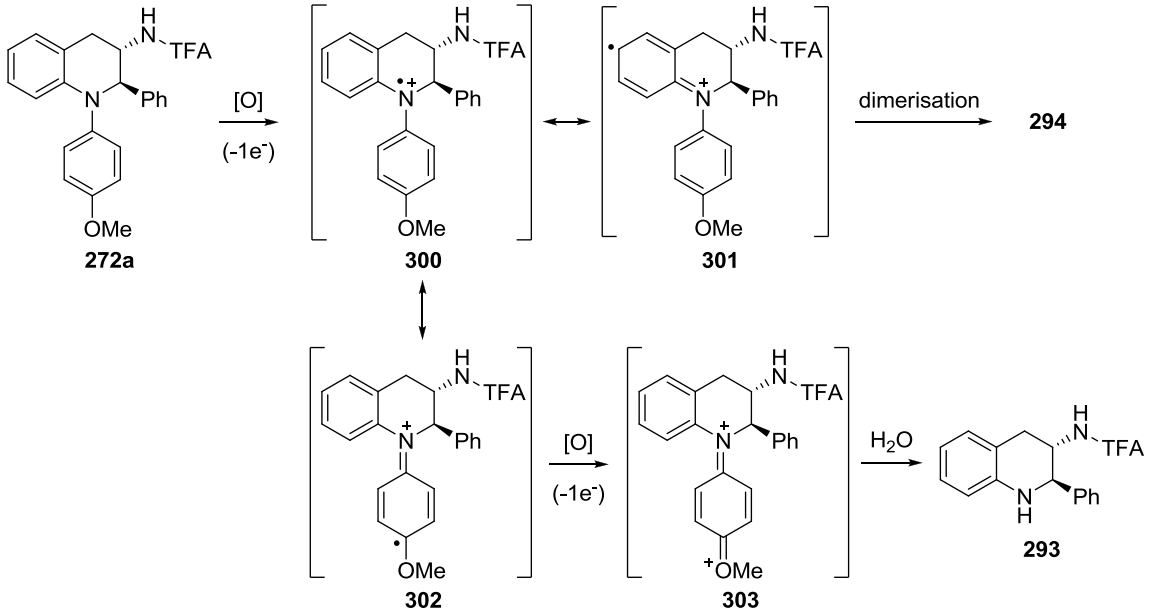
Scheme 112: Attempted PMP deprotection of tetrahydroquinoline **272a** with CAN.

This oxidative coupling reaction has been described previously by the group of Xi.[149] They used similar conditions for the regioselective coupling of *N*,*N*-dialkylarylamines **295** to form the bisaniline products **296** in moderate to good yields (Scheme 113). They propose a mechanism in which initial coordination of the nitrogen atom of aniline **295** to a molecule of CAN is followed by oxidation by a second molecule of CAN to form radical cation **297**. This can then dimerise to give the diiminium intermediate **298** which, after deprotonation, then forms dimer **299**. The formation of bisaniline **296** is accomplished after basic workup.



Scheme 113: Oxidative coupling of *N*,*N*-dialkylarylamines **295**.

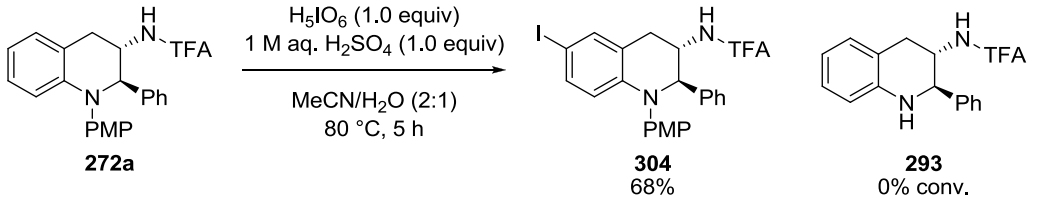
As can be seen in Scheme 112, the C-6 position, *para* to the aryl C–N bond, of tetrahydroquinoline **272a** is highly reactive under oxidising conditions. A possible explanation for the dimerisation reaction being favoured over PMP deprotection is given in Scheme 114. Initial oxidation of tetrahydroquinoline **272a** with a single equivalent of oxidant forms radical cation **300**. This can be drawn in several resonance forms including radical cations **301** and **302**. For PMP deprotection to occur, a second equivalent of oxidant is required to form dicationic species **303**, which can then undergo hydrolysis to form the desired product **293**. However, it appears that the rate of the second oxidation step to form dication **303** is too slow to compete with the dimerisation of radical cation **301** to form dimer **294**. The high reactivity of the C-6 position of tetrahydroquinoline **272a** also caused complications in subsequent PMP deprotection/aromatisation studies.



Scheme 114: Possible oxidation pathways of tetrahydroquinoline **272a**.

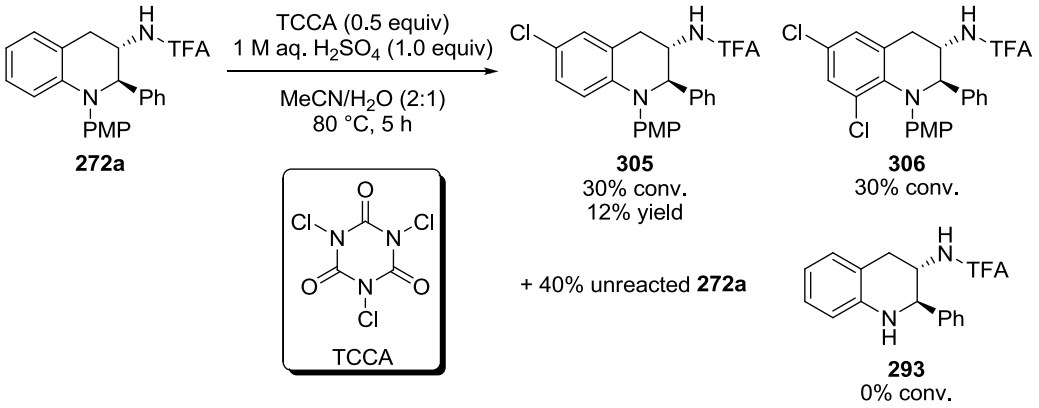
A variety of other oxidants that had previously been successfully applied to PMP deprotections were also tried.[146b] Using 1.0 equiv. of periodic acid (H_5IO_6) and aqueous sulfuric acid produced no reaction at room temperature, but when heated to 80 °C for 5 h complete consumption of tetrahydroquinoline **272a** occurred. Unfortunately none of the desired deprotected product **293** was formed. The only observed product was iodo-tetrahydroquinoline **304**, which was subsequently isolated in 68% yield (Scheme 115). The iodination of activated aromatic groups with periodic acid has been reported previously by Khalilzadeh *et al.*[150] They observed that periodic acid can be readily decomposed on

alumina in aqueous media to produce iodine, which can subsequently be used in iodination reactions. Similar iodinations have also been performed under aqueous acidic conditions.[151]



Scheme 115: Reaction of tetrahydroquinoline **272a** with periodic acid.

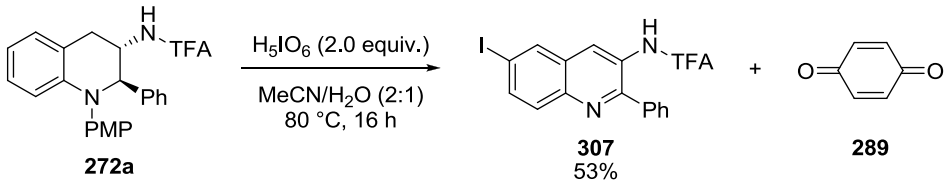
Substituting periodic acid with trichloroisocyanuric acid (TCCA) resulted in 60% conversion of tetrahydroquinoline **272a** to the chlorinated and dichlorinated products **305** and **306**. These two products were formed in approximately 1:1 ratio and the mono-chlorinated product was isolated in 12% yield. As with the periodic acid conditions, no formation of PMP deprotected product **293** was observed (Scheme 116). The formation of the halogenated products **304**, **305** and **306** again highlights the high reactivity of the C-6 position of tetrahydroquinoline **272a** under oxidising conditions.



Scheme 116: Reaction of tetrahydroquinoline **272a** with TCCA.

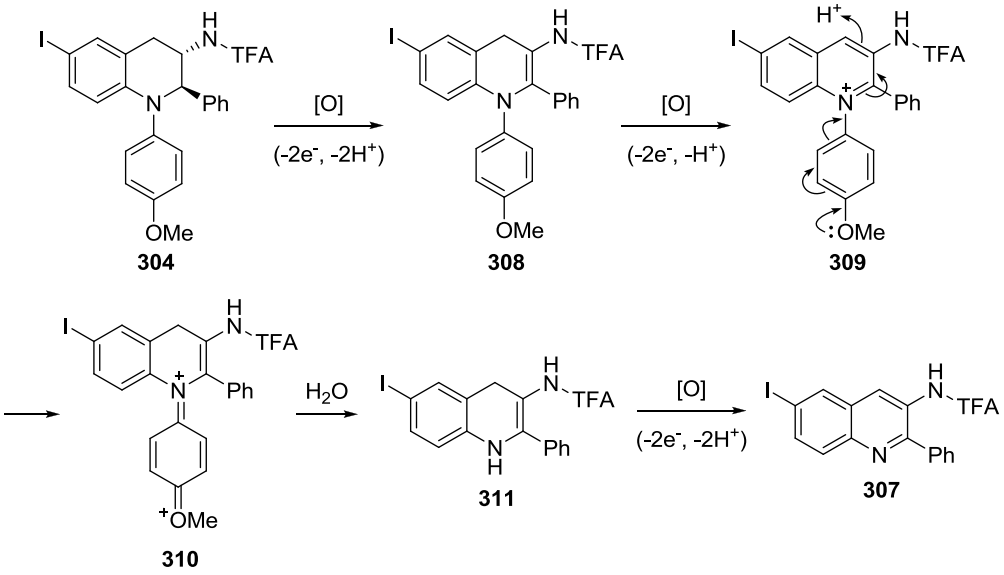
Removal of the PMP group was eventually achieved by increasing the amount of periodic acid from 1.0 to 2.0 equivalents and with a prolonged reaction time of 16 h. This resulted in complete conversion of tetrahydroquinoline **272a** to iodo-quinoline **307** and 1,4-benzoquinone (**289**) (Scheme 117). The reaction was found to be cleaner in the absence of sulfuric acid, providing iodoquinoline **307** in 53% yield. No tetrahydroquinoline products were observed in the crude reaction mixture, with complete oxidation of the tetrahydroquinoline ring to the aromatised quinoline occurring under the reaction

conditions. The use of excess oxidant and extended heating times highlights the forcing conditions that are required to remove the PMP group from tetrahydroquinoline **272a** or the *in situ* formed iodo-tetrahydroquinoline **304**.



Scheme 117: Formation of iodoquinoline **307**.

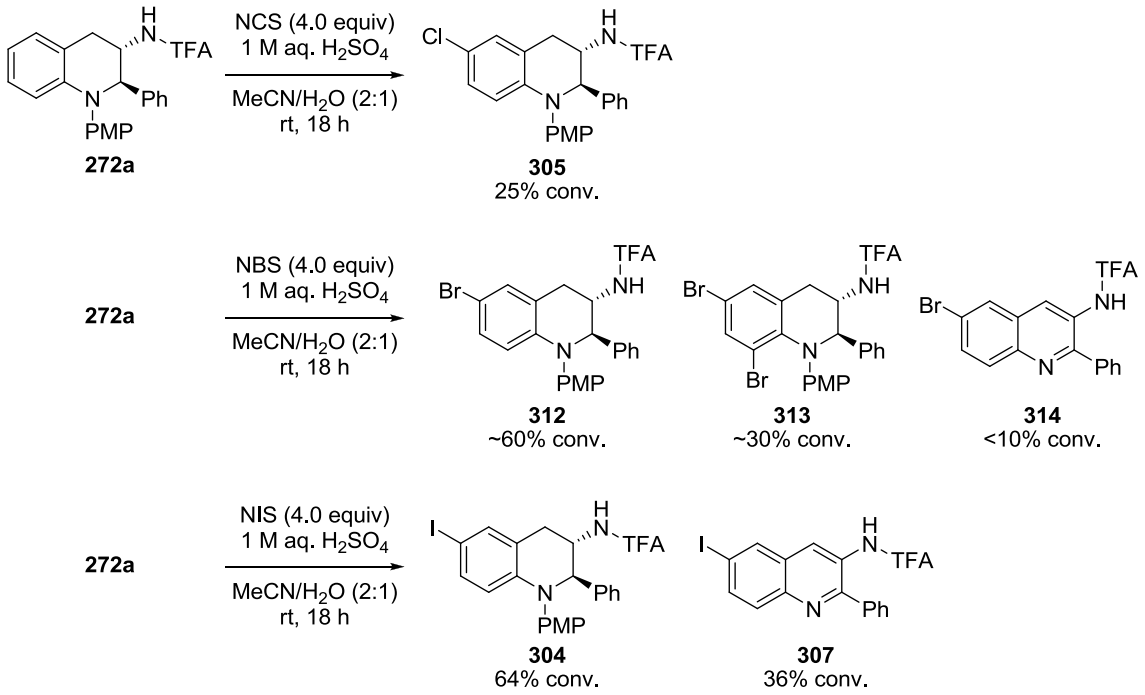
It is not known whether this oxidation reaction proceeds *via* initial removal of the PMP group, followed by aromatisation of the heterocycle, or *via* initial aromatisation of the heterocycle and subsequent PMP deprotection. However, as no PMP deprotected tetrahydroquinoline products have been observed, it seems more likely that the reaction involves initial oxidation of the heterocycle (Scheme 118). Oxidation of tetrahydroquinoline **304** could proceed *via* dihydroquinoline **308** to give quinolinium species **309**. This unstable species can then undergo PMP deprotection by hydrolysis of iminium species **310**. One further oxidation of dihydroquinoline **311** forms the product quinoline **307**.



Scheme 118: Possible PMP deprotection mechanism.

The use of a number of *N*-halosuccinimides to affect PMP deprotection of tetrahydroquinoline **272a** was also investigated (Scheme 119). The use of *N*-chlorosuccinimide (NCS) resulted in 25% conversion to chloro-tetrahydroquinoline **305**,

with no observed PMP deprotection. *N*-Bromosuccinimide (NBS) resulted in complete conversion of the starting material to give approximately 2:1 mixture of mono- and dibromo-tetrahydroquinolines **312** and **313**. These were accompanied by trace amounts of bromo-quinoline **314**. *N*-Iodosuccinimide (NIS) produced conversions of 64% to iodo-tetrahydroquinoline **304** and 36% to iodo-quinoline **307**.

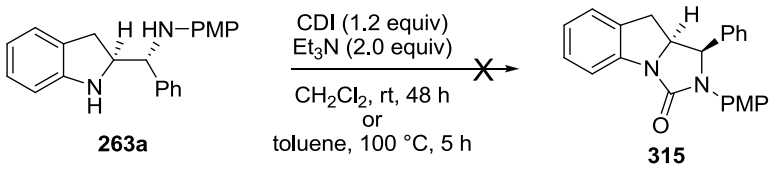


Scheme 119: Attempted PMP deprotection with *N*-halosuccinimides.

Although the formation of these halo-tetrahydroquinoline analogues was undesired, the introduction of halides onto the aromatic ring does provide the opportunity for further elaboration. This late stage functionalisation would be ideal for the introduction of sensitive functional groups that may not tolerate some of the conditions required for the synthesis of tetrahydroquinolines **272**. The failure to selectively cleave the PMP group from tetrahydroquinoline **272a** without also causing complete oxidation to the quinoline products highlights a limitation of the use of PMP protecting groups in the synthesis of these fused heterocycles. To overcome this issue an alternative imine protecting group could be used in the reductive nitro-Mannich reaction. Otherwise, significant effort must be applied to investigating appropriate PMP deprotection methods that may preserve the saturated heterocyclic ring. Similar studies would also be required for the removal of the PMP group from indoline **263a**. Due to time restrictions these studies have not been performed for inclusion in this thesis.

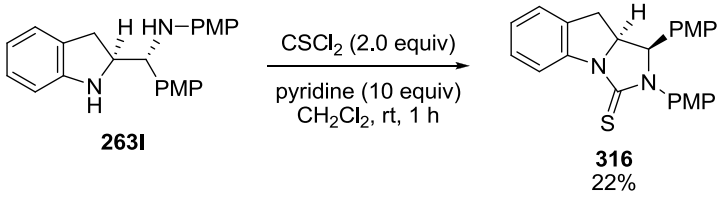
2.6.3 Cyclic Urea Formation

As indoline **263a** is a non-crystalline solid and unstable in solution it was thought that the formation of cyclic ureas would provide products with greater stability and, if they proved to be crystalline solids, would provide the opportunity for X-ray crystal analysis. Consequently, a brief investigation into the synthesis of cyclic ureas of the indoline products was carried out. The formation of cyclic ureas has previously been carried out within our group through the use of phosgene.[106] However, due to the high toxicity of phosgene the use of alternative acylating agents was investigated. Carbonyl diimidazole (CDI) failed to provide any of the desired cyclic urea **315**, with no reaction occurring under the attempted conditions (Scheme 120).



Scheme 120: Attempted formation of cyclic urea **315**.

The formation of cyclic thiourea **316** was achieved by treatment of crude indoline **263l** with thiophosgene. However, the product was isolated in only 22% yield over two steps (Scheme 121). Cyclic thiourea **316** proved to be a stable crystalline solid but all attempts to grow a crystal suitable for X-ray crystal analysis failed.

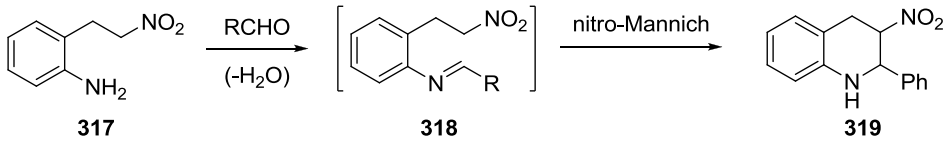


Scheme 121: Synthesis of cyclic thiourea **316**.

Although this was just a brief investigation, further optimisation of these conditions would provide a potentially useful synthesis of these cyclic urea/thiourea products. Furthermore, formation of these stable cyclic products may provide a solution to the difficult purifications associated with particularly unstable indoline products (see Table 10, entries 16-18).

2.7 Intramolecular Nitro-Mannich Reaction

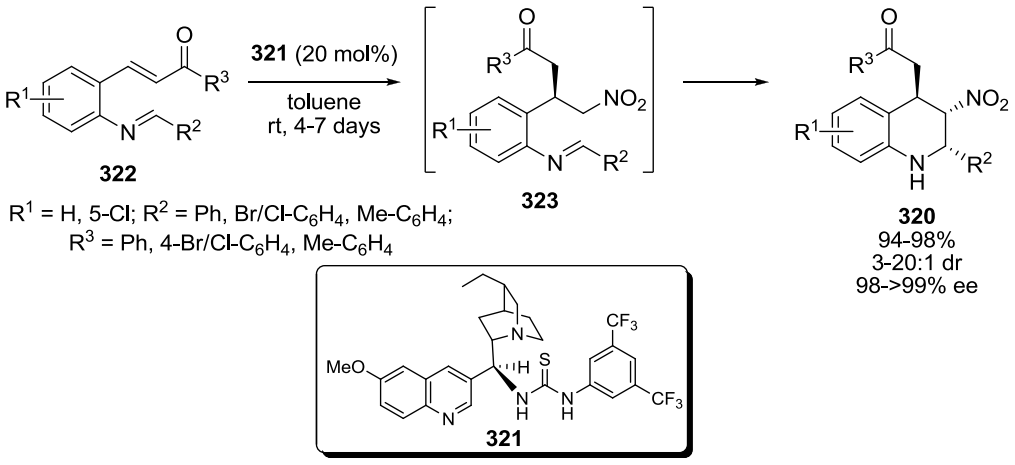
An alternative route to tetrahydroquinoline products that utilised a base-mediated nitro-Mannich reaction was also investigated. We postulated that treatment of nitroalkane **317** with an aldehyde would enable the formation of imine **318** which could then undergo an intramolecular nitro-Mannich reaction forming 3-nitrotetrahydroquinoline **319** (Scheme 122). This tetrahydroquinoline synthesis would also alleviate the problems associated with PMP deprotection. The following sections highlight the results of these investigations.



317 **318** **319**

Scheme 122: Proposed intramolecular nitro-Mannich strategy.

At the outset of this project there had been no reports in the literature of intramolecular nitro-Mannich reactions of this type. However, during our investigations the group of Xu published an asymmetric synthesis of 3-nitrotetrahydroquinolines **320** using an organocatalytic Michael/nitro-Mannich tandem reaction sequence (Scheme 123).[152] The reactions, promoted by thiourea **321**, proceed *via* initial Michael addition of nitromethane to enone **322** and subsequent intramolecular nitro-Mannich reaction of nitroimine **323**. The product tetrahydroquinolines **320** were formed in excellent yield and enantioselectivity, and moderate to good diastereoselectivity for a range of different imine substituents.



322 **323** **320** 94-98% 3-20:1 dr 98->99% ee

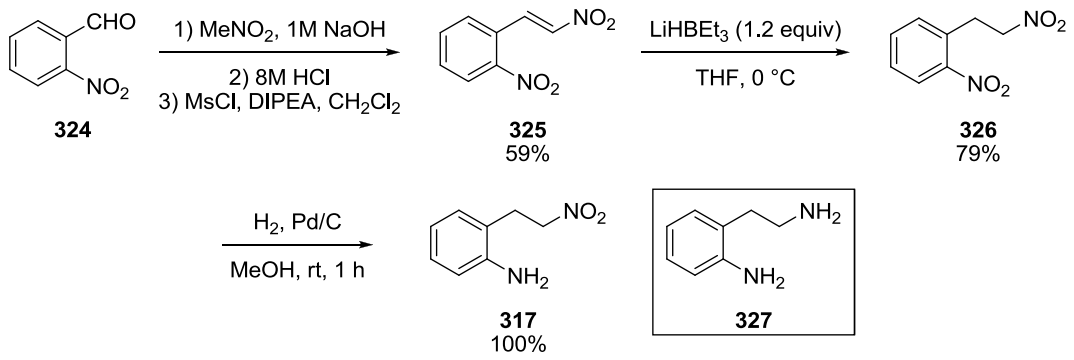
321

Scheme 123: Michael/nitro-Mannich tandem reaction.

The reaction did, however, fail for alkyl-imine analogues such as those derived from ethyl glyoxylate (R^2 = CO_2Et). The reaction also relied on the use of aromatic ketones (R^3 = aryl), as alkyl ketones and esters failed to produce any of the desired products under the reaction conditions. Furthermore, the rate of reaction is slow, with the majority of analogues required almost a week to achieve completion. Considering the limitations of this methodology, we believed that our intramolecular nitro-Mannich reaction would be a valuable alternative for the synthesis of 3-nitrotetrahydroquinolines.

2.7.1 Synthesis of Cylisation Precursor

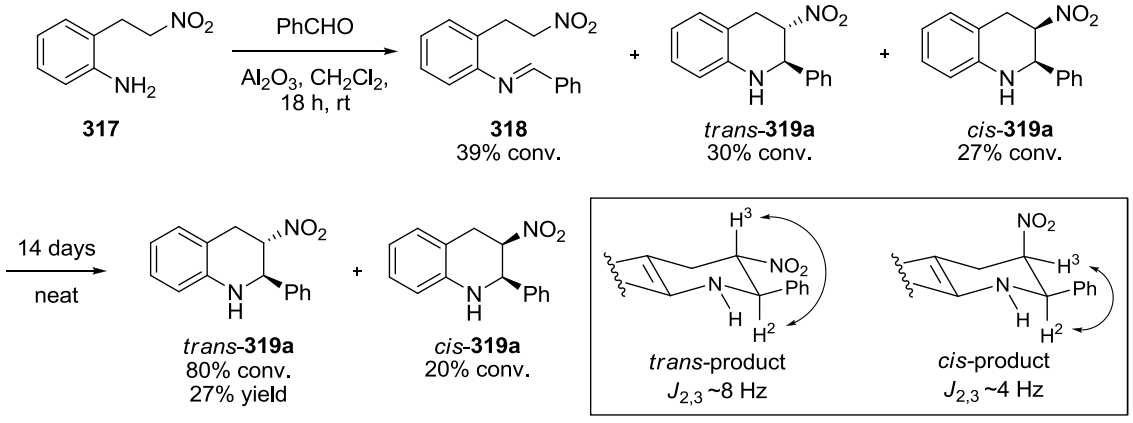
To investigate the intramolecular nitro-Mannich reaction we required a convenient synthesis of nitroalkane **317**. Ideally, we required the use of 2-aminobenzaldehyde, which could be used to synthesise the corresponding nitroalkene. However, due to the propensity of 2-aminobenzaldehyde to undergo polymerisation, 2-nitrobenzaldehyde was used as the aromatic nitro group should be selectivity reduced in the presence of an alkyl nitro group to give the desired product. The synthesis began with a Henry condensation reaction of 2-nitrobenzaldehyde (**324**) with nitromethane to form nitroalkene **325** (Scheme 124). Conjugate reduction of the alkene with $LiHBEt_3$ provided nitroalkane **326**. Although the crude product from this $LiHBEt_3$ reduction appeared pure by ^1H NMR it was found that purification of nitroalkane **326** was necessary to achieve good conversions in the subsequent hydrogenation step. Hydrogenation of nitroalkane **326** over Pd/C for 18 h resulted in reduction of both the aryl and alkyl nitro groups, forming diamino product **327** in quantitative yield. However, selective hydrogenation of the aromatic nitro group could be achieved by careful monitoring of the progress of the reaction, which reached completion after 1 h to provide nitroalkane **317** in quantitative yield. The faster rate of reduction of the aromatic nitro group over the aliphatic nitro group is in agreement with observations made previously by a number of groups using a variety of different reduction methods.[153] With nitroalkane **317** in hand, the intramolecular nitro-Mannich reaction was investigated.



Scheme 124: Synthesis of nitroalkane **317**.

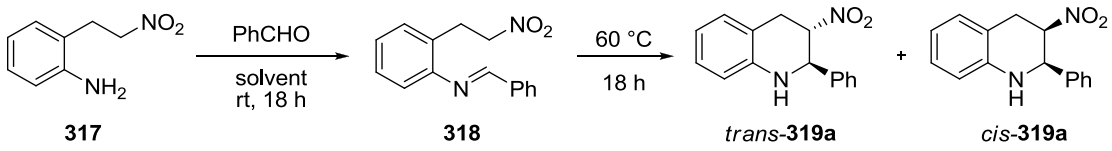
2.7.2 Intramolecular Nitro-Mannich

The formation of imine **318** was first attempted using our standard imine formation protocol, which involves simply stirring a solution of the amine and aldehyde in dichloromethane in the presence of neutral alumina over 18 h. The reaction of nitroalkane **317** with benzaldehyde resulted in a mixture of products which included the desired imine **318**, and the two diastereomers of tetrahydroquinoline **319a** in approximately a 1:1 ratio (Scheme 125). It was found that when left to stand the crude mixture of products gradually performed the nitro-Mannich reaction so that after 14 days the reaction had reached completion. Furthermore, the diastereoselectivity had increased to 80:20. The major product was isolated in 27% yield and was confirmed by ^{1}H NMR to be the *trans* diastereomer of **319a** by comparison of the coupling constants between the H^2 and H^3 protons.



Scheme 125: Synthesis of 3-amino tetrahydroquinoline **319a**.

The effect of solvent on the nitro-Mannich reaction was then investigated. Solutions of nitroalkane **317** and benzaldehyde in a variety of solvents were stirred at rt for 18 h without the addition of a dessicant. NMR analysis showed that in all the solvents used imine **318** was formed in >90% conv., but only trace amounts of tetrahydroquinoline **319a** were formed, and only in protic solvents (Table 11, entries 1 and 2). The reactions were then heated to 60 °C for a further 18 hours. The results highlighted that the use of protic solvents were required to achieve good conversion to tetrahydroquinoline **319a**, with only EtOH and MeOH giving good conversions (Table 11, entries 1 and 2). The use of aprotic solvent led to only trace amounts of the desired product (Table 11, entries 3-7). Unfortunately, the conversions of the reactions did not reflect the diastereoselectivities, with those performed in protic solvents resulting in unselective product formation. The aprotic solvents appeared to give much better selectivities, albeit at the expense of yield. Regardless, the promising conversions obtained in MeOH and EtOH provided the opportunity to improve the selectivities by investigating the effect of various additives.



317 **318** *trans*-**319a** *cis*-**319a**

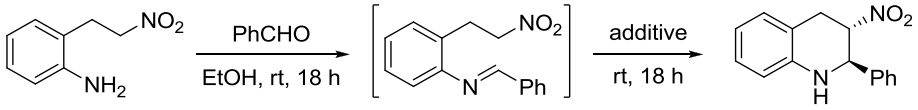
Entry	Solvent	% conv. after 18 h at rt[a]		% conv. after 18 h at 60 °C[a]	
		318	**319a**[b]	**318**	**319a**[b]
1	EtOH	95	3 (50:50)	12	88 (50:50)
2	MeOH	90	7 (50:50)	4	96 (50:50)
3	DCM	>95	0	97	3 (85:15)
4	toluene	>95	0	97	3 (90:10)
5	THF	>95	0	98	2 (95:5)
6	Et_2O	>95	0	98	2 (90:10)
7	DME	>95	0	97	3 (90:10)

[a] Determined by ^{1}H NMR. [b] Numbers in parenthesis shows *trans*:*cis* ratio.

Table 11: Effect of solvent on the intramolecular nitro-Mannich reaction.

Subsequent investigations into this intramolecular nitro-Mannich reaction were performed in collaboration with Pascual Ribelles, who investigated the effect of a variety of additives

on the reaction (Table 12). Initial formation of imine **318** in EtOH at rt over 18 h was followed by the introduction of a number of additives. Activation of the imine nitrogen with various Lewis acids was attempted but these proved unsuccessful as no improvement to either yield or selectivity was observed (Table 12, entries 1-4). The application of Brønsted bases to activate the nitro group proved to be more successful. Triethylamine gave complete conversion to tetrahydroquinoline **319a** with a slightly improved *trans*:*cis* ratio of 60:40 (Table 12, entry 6). It was found that the addition of 3.0 equiv. of aqueous ammonia to imine **318** enabled the formation of tetrahydroquinoline **319a** in excellent yield and diastereoselectivity (Table 12, entry 7).



317 **318** **319a**

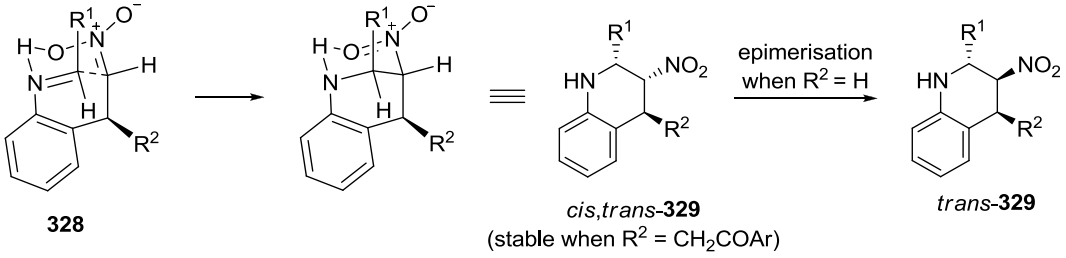
Entry	Additive	Conversion (%)[d]	dr (*trans*:*cis*)[d]
1[a,b]	$AlCl_3$	<10	-
2[a,b]	CAN	<10	-
3[a,b]	$TiCl_4$	<10	-
4[a,b]	$Zn(OTf)_2$	<10	-
5[a,c]	DIPEA	<10	-
6[a]	Et_3N	>95	60:40
7[a]	aq. NH_3	>95	90:10

[a] Reactions performed by P. Ribelles. [b] Imine **318** recovered. [c] Degradation of imine **318** occurred. [d] Determined by ^1H NMR.

Table 12: Effect of additives on the formation of tetrahydroquinoline **319a**.

It was discovered that the high diastereoselectivities achieved in the reaction with ammonia are achieved by an epimerisation process. Workup of the reaction after only 3 h revealed 50% conv. to tetrahydroquinoline **319a** with a 1:1 ratio of diastereomers, whereas complete conversion and >90:10 selectivity was achieved after 18 h. This suggests that the reaction proceeds *via* initial unselective ring closure. Epimerisation to the thermodynamic *trans*-product then occurs over approximately 18 h. Xu *et al.* found that the major product of their intramolecular nitro-Mannich reactions possessed a *cis* relationship between the

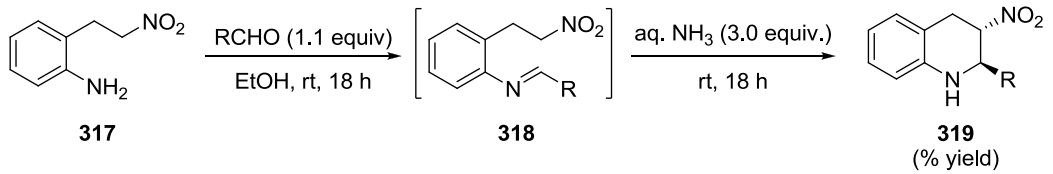
NO_2 group and the imine substituent (see Scheme 123).[152] They proposed the mechanism shown in Scheme 126 which proceeds *via* chair TS **328** to give *cis*,*trans*-**329**. It would appear that the presence of the R^2 substituent renders this configuration stable under their reaction conditions. However, in our system, when R^2=H, epimerisation occurs to give the thermodynamic product with the R^1 and NO_2 groups in a *trans* configuration. This epimerisation process could occur either by a retro-nitro-Mannich process or by deprotonation α to the nitro group, both of which are likely to be facilitated by the presence of excess base. The stability of the kinetic *cis*,*trans*-products generated by Xu *et al.* (when R^2 = CH_2COAr) could result from the presence of the R^2 substituent and the catalytic, as opposed to stoichiometric, amount of base used in their reaction conditions, which are likely to slow/prevent the epimerisation process.



Scheme 126: Mechanism of intramolecular nitro-Mannich reaction.

2.7.3 Substrate Scope

With the successful formation of 3-nitrotetrahydroquinoline **319a** in excellent yield and diastereoselectivity, the scope of the intramolecular nitro-Mannich reaction was investigated. This was first carried out by reacting a variety of different aldehydes with nitroalkane **317**, the results of which are shown in Table 13. The products were formed in good to excellent yield and with excellent *trans*-diastereoselectivity for all aryl aldehydes tested, including electron rich and poor, and *ortho*-substituted examples (Table 13, entries 1-13). The reaction proved less tolerant of alkyl aldehydes, with cyclohexane carboxaldehyde giving product **319n** in a lower yield of 65% but still with good *trans* selectivity (Table 13, entry 14). Ethyl glyoxylate was found to undergo the nitro-Mannich reaction but with only 70% conversion after 18 h and with a significantly lower *trans*:*cis* ratio of 60:40 (Table 13, entry 15).



317 **318** **319** (% yield)

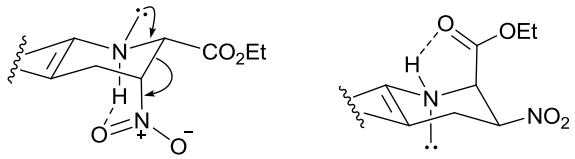
Entry	R	Product	Yield (%)[b]	dr (*trans*:*cis*)[d]
1[a]	Ph	**319a**	82	90:10
2[a]	4-CF_3-C_6H_4	**319b**	94	90:10
3[a]	4-Br-C_6H_4	**319c**	70	90:10
4[a]	4-NO_2-C_6H_4	**319d**	72	85:15
5[a]	4-Me-C_6H_4	**319e**	80	85:15
6[a]	4-MeO-C_6H_4	**319f**	86	90:10
7[a]	3-Cl-C_6H_4	**319g**	84	90:10
8[a]	3-MeO-C_6H_4	**319h**	83	90:10
9[a]	3,5-Cl_2-C_6H_3	**319i**	89	90:10
10[a]	2-Me-C_6H_4	**319j**	92	>95:5
11[a]	2-CF_3-C_6H_4	**319k**	93	95:5
12[a]	2-Cl-C_6H_4	**319l**	92	>95:5
13[a]	2-Br-C_6H_4	**319m**	90	>95:5
14	cyclohexyl	**319n**	65	90:10
15	CO_2Et	**319o**	0 (70)[c,d]	60:40

[a] Reactions performed by P. Ribelles. [b] Isolated yields. [c] Number in parenthesis shows conversion of nitroalkane **317** in the crude product. [d] Determined by ^{1}H NMR.

Table 13: Scope of the intramolecular nitro-Mannich reaction.

The poor conversion to tetrahydroquinoline **319o** with ethyl glyoxylate was attributed to the lower stability of product **319o**, which underwent complete degradation during purification by column chromatography. The lower *trans* selectivity obtained for this analogue could be due to competing hydrogen-bonding interactions between the N–H group and either the nitro or ester groups (Figure 22). If the epimerisation process is proceeding *via* a retro-nitro-Mannich process, successful epimerisation will only occur when efficient orbital overlap between the nitrogen lone pair and the HNC–CNO_2 bond is achieved, as is the case when the nitrogen lone pair is in an equatorial position (see **319o-E**,

Figure 22). This conformer is favoured due to a hydrogen bonding interaction between the N–H and ON–O groups. With ester analogue **319o** a competing hydrogen bonding interaction between the N–H and OC=O groups occurs, which forces the nitrogen lone pair into an axial position and minimises the orbital overlap between the nitrogen lone pair and NC–CN (see **319o-A**, Figure 22). This competition between hydrogen-bonded conformations, which does not occur in analogues **319a-n**, stabilises the *cis* diastereomer to retro-addition and hence slows epimerisation to give poor diastereoselectivity. An alternative possibility is that the retro-addition reaction is slower due to the lower stability the retro-addition product, imine **318o**. Furthermore, the low A-value of the CO_2Et group (~1.2 kcal/mol) could further slow the rate of epimerisation to the thermodynamic *trans* product. The result of these effects would be that the reaction to form tetrahydroquinoline **319o** is under kinetic control, unlike the other examples whose high selectivity arises from a thermodynamic epimerisation process.



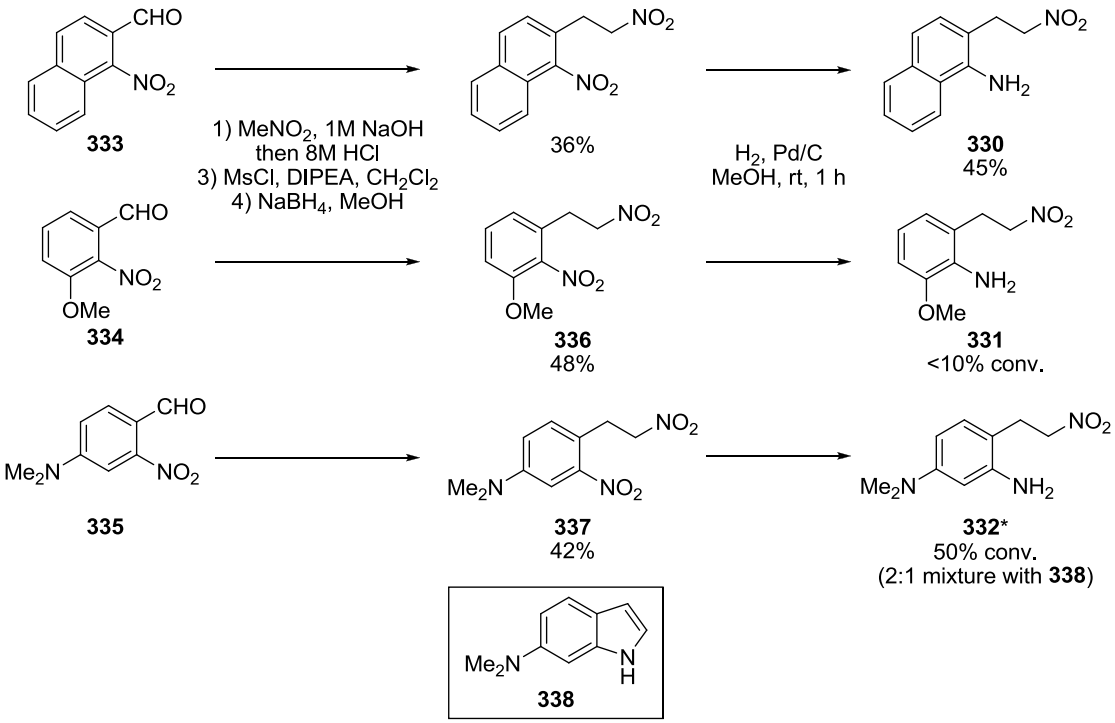
319o-E
equatorial lone pair positioned for retro-addition

319o-A
axial lone pair leads to inefficient orbital overlap

Figure 22: Possible conformations of tetrahydroquinoline **319a**.

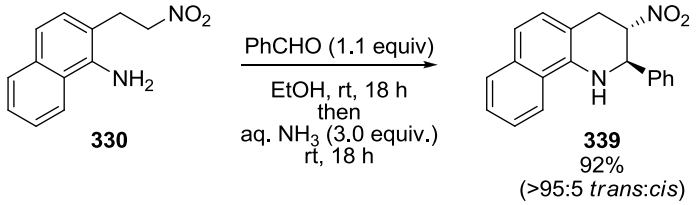
The use of more functionalised analogues of nitroalkane **317** was also investigated. Using the same synthesis that was used for nitroalkane **317** the syntheses of nitroalkanes **330**, **331** and **332** were attempted (Scheme 127). The synthesis of naphthalene analogue **330** was accomplished in 16% overall yield from aldehyde **333**. The use of electron rich 2-nitrobenzaldehydes **334** and **335** for the synthesis of their respective nitroalkanes proved problematic. This was due to difficulties arising from the selective reduction of the aryl nitro groups of nitroarenes **336** and **337**. Methoxy-nitroalkane **336** was successfully synthesised from 3-methoxy-2-nitrobenzaldehyde (**334**) but failed to undergo selective reduction of the aryl nitro group, as only very low conversions to the desired product were achieved. Dimethylamino-nitroalkane **337** was formed from 4-dimethylamino-2-nitrobenzaldehyde (**335**). When submitted to the hydrogenation conditions complete reduction of the aryl nitro group was achieved, albeit with approximately 25% over-reduction to the diamine product, but upon purification by column chromatography

the formation of indole **338** was observed. We were unable to separate indole **338**, formed by a Nef reaction followed by intramolecular amination, from our desired product. Nitroalkanes **331** and **332** were, therefore, not applied to the intramolecular nitro-Mannich reaction. Further studies are required to develop a more general synthesis of the nitroalkane substrates for use in these intramolecular nitro-Mannich reactions. Due to time constraints these investigations were not performed for inclusion in this thesis.



Scheme 127: Attempted synthesis of analogues of nitroalkane **317**.

The successfully formed nitroalkane **330** was then applied to the intramolecular nitro-Mannich reaction (Scheme 128). The reaction with benzaldehyde provided tetrahydroquinoline **339** in excellent yield and diastereoselectivity. This example demonstrates that the reaction still performs well when sterically crowded anilines are used.



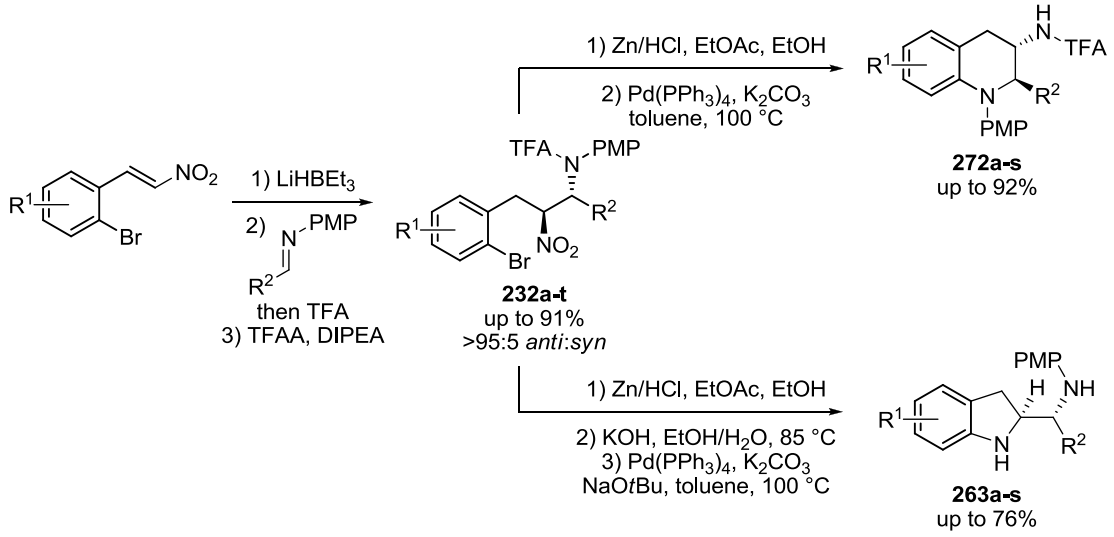
Scheme 128: Formation of tetrahydroquinoline **339**.

This intramolecular nitro-Mannich methodology provides a convenient method for the synthesis of 3-nitrotetrahydroquinolines in high yield and diastereoselectivity. Although limitations do exist with respect to the effective synthesis of the nitroalkane substrates and the use of alkyl aldehydes, it represents a complimentary method to that reported by Xu *et al.*, with our synthesis being highly selective for the *trans*-3-nitrotetrahydroquinolines. Furthermore, the successful application of asymmetric organocatalysis by Xu *et al.* provides encouragement for us to render our synthesis asymmetric using similar organocatalysts in the future.

Chapter 3: *Conclusions and Future Studies*

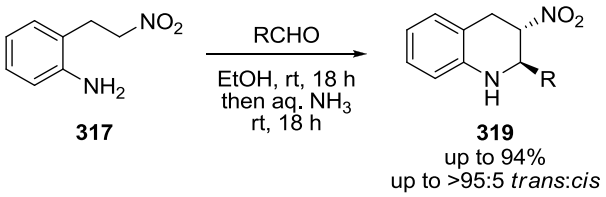
3.1 Conclusions

The previous chapter in this thesis has presented the results obtained from our investigations into the synthesis of fused nitrogen heterocycles through the use of the nitro-Mannich reaction. Firstly, a high yielding and highly diastereoselective synthesis of 2-aminomethylene indolines **263** and 3-aminotetrahydroquinolines **272** was reported (Scheme 129). This was achieved by utilising a reductive nitro-Mannich reaction of nitroalkenes bearing a pendant *ortho*-bromo-substituted aromatic ring. Reduction of the *β*-nitroamine products **232** to the 1,2-diamines provided the substrates for selective intramolecular *N*-arylations to yield both five- and six-membered ring heterocycles. This synthesis was used to produce an array of 1,2-diamine-containing fused heterocycles.



Scheme 129: Synthesis of fused nitrogen heterocycles.

Secondly, an alternative nitro-Mannich reaction was applied to the synthesis of tetrahydroquinolines. This involved a tandem amination/intramolecular nitro-Mannich reaction between nitroalkane **317** and a variety of aldehydes (Scheme 130). Initial imine formation followed by a nitro-Mannich 6-*endo*-trig cyclisation furnished 3-aminotetrahydroquinolines in excellent yields and with high diastereoselectivity for the *trans* products. The high diastereoselectivity was found to arise from an epimerisation process to give the thermodynamic product.

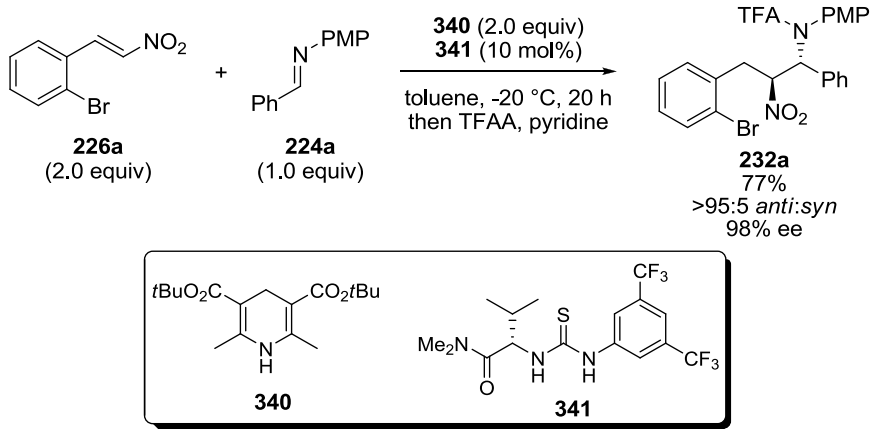


Scheme 130: Synthesis of 3-aminotetrahydroquinolines.

The development of these two new methodologies has enabled us to extend the scope of the nitro-Mannich reaction by demonstrating its synthetic utility through the generation of a variety of important fused heterocyclic products. The following section will present some of the possible future avenues of research that could be performed as an extension to the work that has already been presented in this thesis.

3.2 Future Studies

One possible improvement to the current reductive nitro-Mannich/*N*-arylation methodology for the synthesis of fused heterocycles would be to develop an asymmetric variant. This would require the use of an asymmetric reductive nitro-Mannich reaction, enabling the synthesis of a range of indoline and tetrahydroquinoline products in enantioenriched form. Preliminary work by Paul Koovits in our group has shown that it is possible to perform highly enantioselective reductive nitro-Mannich reactions by utilising chiral thiourea organocatalysis.[154] The reaction involves a tandem hydride conjugate addition nitro-Mannich reaction using dihydropyridine **340** as the hydride source (Scheme 131). The reaction is catalysed by thiourea **341** which promotes the conjugate addition reaction and controls the approach of the imine to the resulting nitronate. The nitro-Mannich products are formed in excellent yield and diastereo- and enantioselectivity. The reaction was also used to form *β*-nitroacetamide **232a** in excellent enantioselectivity. Subsequent reduction and intramolecular *N*-arylation of this product would generate highly enantioenriched fused heterocycles.

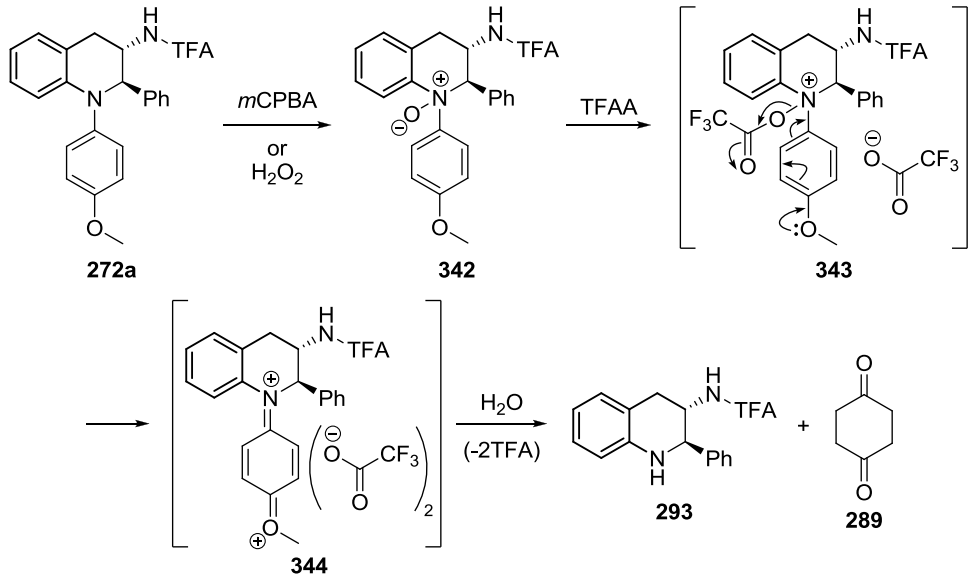


Scheme 131: An asymmetric reductive nitro-Mannich reaction.

Similarly, based on the successful work by Xu *et al.* on thiourea catalysed intramolecular nitro-Mannich reactions,[152] it seems plausible that asymmetric organocatalysis could also be applied to our intramolecular nitro-Mannich reaction. However, for this reaction to be of greater synthetic utility an improved synthesis of analogues of nitroalkane **317** would be required.

Due to the problems associated with the removal of the PMP group from our fused heterocyclic products, alternative deprotection methods must be sought. These would require the use of oxidants that can selectively oxidise the PMP group without also oxidising the fused heterocycle, causing aromatisation. Although several alternative methods are available, including anodic oxidations,[146a] which have been used by Mioskowski *et al.* to perform highly selective deprotections that failed when using CAN; and enzymatic deprotections,[146c] no examples of the removal of PMP groups from anilines or nitrogen heterocycles have been reported. As a result, these methods may also present the same problems that have already been observed during the PMP deprotections attempted in this thesis.

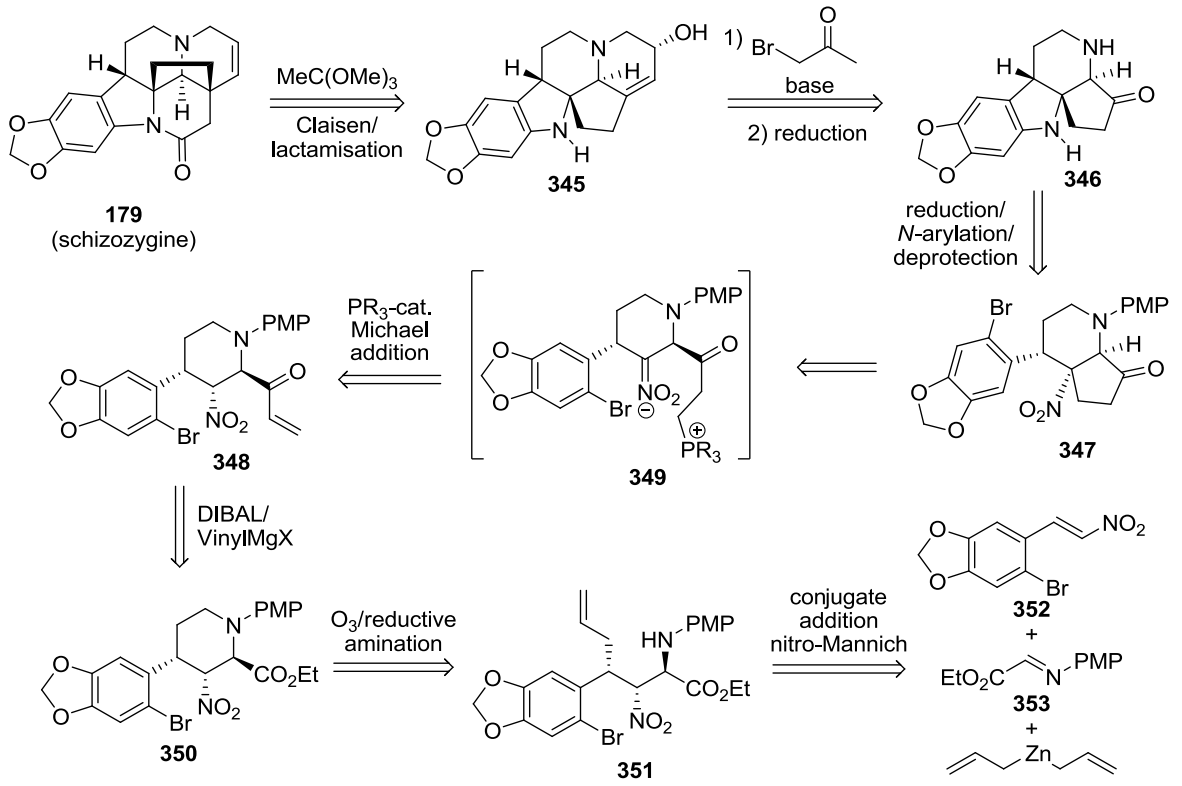
Investigations into alternative deprotection strategies that do not require the use of single electron oxidants could also be performed. One possible method is the Polonovski reaction (Scheme 132).[155] This would require the selective oxidation of the tertiary amine over the secondary trifluoroacetamide in **272a** to form *N*-oxide **342**. Treatment with TFAA then results in *O*-acylation, forming trifluoroacetate ester **343**, which could eliminate a trifluoroacetate anion to give intermediate **344**. Hydrolysis during workup would then give the desired deprotected product **293**. Although Polonovski reactions have not been used previously for such deprotection reactions, the mechanism seems plausible and provides a potential alternative to well established methods.



Scheme 132: PMP deprotection *via* a Polonovski reaction.

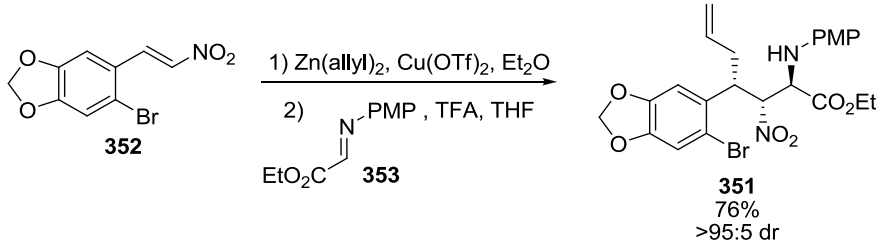
If selective removal of the PMP group cannot be achieved it may be necessary to use alternative imine protecting groups in the reductive nitro-Mannich reaction. These could include protecting groups that do not require oxidising conditions for removal. Alternatively, it would be possible to use an imine that possesses the *N*-functionality that is required in the final heterocyclic product, therefore, avoiding the need to carry out a deprotection procedure. However, this functionality would need to be inert to the reaction conditions using during the heterocycle synthesis, so may be limited to fairly neutral groups such as alkyl or aryl.

This 1,2-diamine-containing fused heterocycle synthesis could also be applied to the synthesis of an appropriate natural product. Schizozygine (**179**, see Figure 10, Section 1.6.1) contains a 2-aminomethylene indoline core making it an ideal target to demonstrate the synthetic utility of our methodology.[113] A possible retro-synthetic analysis is given in Scheme 133. The lactam ring and final quaternary centre would be introduced *via* a Johnson-Claisen/lactamisation sequence from allylic alcohol **345**. An *N*-alkylation/aldol condensation followed by a hydride reduction would form **345** from aminoketone **346**, itself formed by a reduction/*N*-arylation sequence from *β*-nitroamine **347**. To form the five-membered ring ketone we would require a disfavoured 5-*endo*-trig cyclisation of the nitroalkane to the vinyl ketone in **348**. We hypothesised that the use of catalytic phosphine would enable the formation of intermediate **349** which could then undergo a favourable 5-*exo*-tet cyclisation to form **347**. Piperidine **350** would be formed *via* an ozonolysis/reductive amination sequence from *β*-nitroamine **351**. The first step in the synthesis would be a conjugate addition nitro-Mannich reaction between diallylzinc, nitroalkene **352**, and glyoxylate imine **353**.



Scheme 133: Retro-synthetic analysis of schizozygine **179**.

Preliminary studies have shown that this diallylzinc conjugate addition nitro-Mannich reaction can be used to form *β*-nitroamine **351** (Scheme 134). A $Cu(OTf)_2$-catalysed conjugate addition of diallylzinc to nitroalkene **352** is followed by the addition of glyoxylate imine **353** and TFA to yield **351** in 76% yield and with >95:5 selectivity for the desired diastereomer. This reaction provides a starting point for a racemic synthesis of schizozygine **179**, however, due to the high reactivity of diallylzinc an alternative allyl nucleophile may be required to render the synthesis asymmetric. This will be a challenging reaction as there are only several examples of asymmetric conjugate allylations in the literature, with none that involve nitroalkenes.[156]



Scheme 134: Preliminary studies into the synthesis of schizozygine **179**.

Chapter 4: *Experimental*

4.1 General Experimental Details

For all non-aqueous chemistry, glassware was flame dried and reactions were carried out under an inert (N_2) atmosphere. Cooling to 0 °C was affected using an ice-water bath. Cryogenic conditions (-78 °C) were achieved using a solid CO_2-acetone bath. For the purpose of thin layer chromatography, Polygram® SilG/UV_{254} 0.25 mm silica gel plates were used. Visualisation was achieved using ultraviolet light (254 nm) and/or a $KMnO_4$ solution. Removal of solvents *in vacuo* was achieved using a water aspirator/house vacuum and Büchi rotary evaporators. Flash column chromatography was performed using Gedran® silica gel 60, 40-63 μm.

4.2 Analytical Instruments and Characterisation

All ^{1}H, ^{19}F and ^{13}C NMR data were recorded using Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz and Bruker AVANCE 600 MHz spectrometers. Data was manipulated directly using Bruker XwinNMR (version 2.6) or Topspin (version 2.1). Samples were made as dilute solutions of $CDCl_3$ unless otherwise stated. All chemical shifts (δ) are reported in parts per million relative to residual solvent peaks. δ 7.27 for ^{1}H NMR and δ = 77.2 for ^{13}C NMR in $CDCl_3$. Multiplicities for ^{1}H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). COSY, DEPT, HMQC and HMBC experiments were carried out to aid assignment.

Mass spectra were acquired on Thermo Finnigan Mat900xp (EI/CI), VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system. X-ray crystallography was carried out using a Bruker SMART APEX CCD diffractometer.

4.3 Purification of Solvents and Reagents

Commercial solvents and reagents were used as supplied or purified in accordance with standard procedures.[157]

Dichloromethane (CH_2Cl_2) was obtained from a solvents tower, where degassed dichloromethane was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diethyl ether (Et_2O) was obtained from a solvents tower, where degassed diethyl ether was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Di*iso*propylamine ($^{i}Pr_2NH$) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Potassium carbonate (K_2CO_3) was dried by heating under high vacuum.

Sodium *tert*-butoxide ($NaO^{t}Bu$) was dried by heating under high vacuum.

Tetrahydrofuran (THF) was obtained from a solvents tower, where degassed tetrahydrofuran was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Toluene was obtained from a solvents tower, where degassed toluene was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Triethylamine (Et_3N) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

All solutions of organolithium reagents were standardised with diphenylacetic acid or *N*-benzylbenzamide.

Activation of 4 Å molecular sieves was achieved by heating under high vacuum.

4.4 Experimental Procedures

4.4.1 Preparation of Nitroalkenes

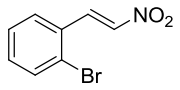
General Procedure A

A mixture of benzaldehyde (1.00 mmol) and NH_4OAc (1.00 mmol) in $MeNO_2$ (90.0 mmol) was heated to 100 °C for 1-3 h or until the reaction was complete by TLC. The reaction was allowed to cool to rt and H_2O (10 mL) was added. The product was extracted into EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude nitroalkene which was purified by column chromatography.

General Procedure B

To a solution of 2-nitrobenzaldehyde (1.00 mmol) and nitromethane (2.50 mmol) in MeOH (0.50 mL) at 0 °C was added aq. 1 M NaOH (2.50 mmol) by addition funnel while maintaining an internal reaction temperature of 10-15 °C. Ice water (1.80 mL) was added and the reaction was stirred at 0 °C for 15 min. The reaction mixture was slowly added to aq. 8 M HCl (14.0 mmol) at 0 °C before being allowed to warm to room temperature and stirred for 18 h. The product was extracted into dichloromethane (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture consisting of nitroalcohol and nitroalkene. This crude mixture was dissolved in CH_2Cl_2 (2.0 mL) and cooled to 0 °C. MsCl (1.00 mmol) was added dropwise and stirred for 5 min before the dropwise addition of DIPEA (2.00 mmol) over 5 min. The resulting solution was allowed to warm to rt over 18 h before adding H_2O (10 mL). The product was extracted into CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with aq. 2 M HCl (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude nitroalkene, which was purified by flash column chromatography or recrystallisation.

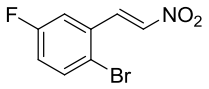
1-Bromo((*E*)-2-nitrovinyl)benzene (226a)



226a

To a solution of 2-bromobenzaldehyde (9.02 g, 48.8 mmol) and nitromethane (6.64 mL, 122 mmol) in MeOH (21 mL) at 0 °C was added aq. 1 M NaOH (122 mL, 122 mmol) by addition funnel while maintaining an internal reaction temperature of 10-15 °C. Ice water (85 mL) was added and the reaction was stirred at 0 °C for 15 min. The reaction mixture was slowly added to aq. 8 M HCl (114 mL, 683 mmol) at 0 °C before being allowed to warm to room temperature and stirred for 18 h. The product was extracted into dichloromethane (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude nitroalkene **226a** as a yellow solid. Purification by recrystallisation from Et_2O yielded pure **226a** as a yellow solid (8.05 g, 72%); mp 86-88°C (lit.[158] 88-91 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, m, Ar*H*), 7.55 (1H, d, *J* = 13.7, C*H*Ar), 7.58 (1H, d, *J* = 7.6, Ar*H*), 7.70 (1H, d, *J* = 7.8, Ar*H*), 8.41 (1H, d, *J* = 13.7, C*H*NO_2). NMR data are consistent published data.[158]

1-Bromo-4-fluoro-2-((*E*)-2-nitro-vinyl)-benzene (226b)

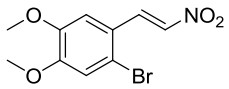


226b

Prepared using general procedure A. 2-Bromo-5-fluorobenzaldehyde (131 mg, 0.645 mmol) gave crude nitroalkene **226b** as a yellow/brown oil. Purification by flash column chromatography (10% Et_2O/Pet. ether) yielded pure **226b** as a yellow solid (109 mg, 68%); mp 78-80 °C; R_f 0.50 (10% Et_2O/Pet. ether); IR υ_{max} (neat) 3116-2973 (C-H), 1635 (N-O), 1520 (C=C), 1463 (C=C), 1344 (N-O), 1269 (C-F) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, ddd, *J* = 8.9, 7.6, 3.0, Ar*H*), 7.29 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 7.51 (1H, d, *J* = 13.7, C*H*NO_2), 7.67 (1H, ddd, *J* = 8.9, 5.2, Ar*H*), 8.33 (1H, dd, *J* = 13.7, 1.0, C*H*Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 115.3 (1C, d, *J* = 24.1, Ar*C*H), 120.4 (1C, d, *J* = 22.9, Ar*C*H), 120.7 (1C, d, *J* = 3.3, Ar*C*Br, 132.0 (1C, d, *J* = 8.0, Ar*C*CH), 135.5 (1C, d, *J* = 8.0, Ar*C*H), 136.7 (1C, d, *J* = 2.0, *C*HAr), 139.8 (1C, s, *C*HNO_2), 161.9 (1C, d, *J* = 249.6, Ar*C*F); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (1F, q, *J* = 7.1, Ar*F*); m/z (EI) 245+247 (1:1, 11%, M^+), 198+200 (19%, M^+-NO_2), 166 (51%, M^+-Br), 120 (100%, M^+(Br+NO_2); HRMS

$C_8H_5BrFNO_2$ calcd. 244.9482, found 244.9494; Anal. calcd. for $C_8H_5BrFNO_2$: C, 39.05; H, 2.05; N, 5.69; found: C, 39.03; H, 1.88; N, 5.38%.

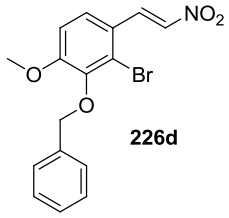
1-Bromo-4,5-dimethoxy-2-((*E*)-2-nitrovinyl)benzene (226c)



226c

Prepared using general procedure A. 2-Bromoveratraldehyde (97 mg, 0.40 mmol) gave crude nitroalkene **226c** as a yellow solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure **226c** as a yellow solid (102 mg, 89%); mp 162-164 °C; R_f 0.37 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3104-2843 (C-H), 1597 (N-O), 1511 (C=C), 1496 (C=C), 1331(N-O), 1268, 1214 (C-O), 1170cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (3H, s, OC*H*$_3$), 3.95 (3H, s, OC*H*$_3$), 6.99 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*), 7.52 (1H, d, *J* = 13.6, C*H*Ar), 8.37 (1H, d, *J* = 13.6, C*H*NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 56.2 (O*C*H_3), 56.4 (O*C*H_3), 109.5 (Ar*C*H), 116.0 (Ar*C*H), 119.3 (Ar*C*), 122.0 (Ar*C*), 136.9 (*C*HCHNO_2), 137.8 (*C*HNO_2), 148.9 (Ar*C*O), 152.9 (Ar*C*O); m/z (EI) 287+289 (22%, M^+), 240+242 (11%, M^+-NO_2), 208 (51%, M^+-Br); HRMS $C_{10}H_{10}BrNO_4$ calcd. 286.9788, found 286.9785; Anal. calcd. for $C_{10}H_{10}BrNO_4$: C, 41.69; H, 3.50; N, 4.86; found: C, 41.99; H, 3.55; N, 4.56%.

3-Benzyloxy-2-bromo-4-methoxy-*β*-nitrostyrene (226d)

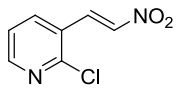


226d

To a yellow suspension of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (301 mg, 1.30 mmol) and K_2CO_3 (540 mg, 3.91 mmol) in dry EtOH at rt was added BnCl (225 μL, 1.95 mmol). The mixture was heated at reflux and stirred for 4 h before being left to cool to rt over 16 h. The reaction was filtered through Celite® and concentrated *in vacuo*. The residue was diluted with EtOAc (20 mL) and washed with aq. 2 M HCl (10 mL), brine (10 mL) dried ($MgSO_4$) and concentrated *in vacuo* to give crude 3-benzyloxy-2-bromo-4-methoxybenzaldehyde. Purification by flash column chromatography (15% EtOAc/Pet. ether) gave pure 3-benzyloxy-2-bromo-4-methoxybenzaldehyde as a white solid (410 mg,

98%); mp 71-72 °C (lit.[159] 79-81 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (3H, s, OC*H*$_3$), 5.06 (2H, s, C*H*$_2$Ph), 6.99 (1H, d, *J* = 8.7, Ar*H*), 7.35-7.42 (3H, m, Ar*H*), 7.56 (2H, d, *J* = 7.1, Ar*H*), 7.77 (1H, d, *J* = 8.6, Ar*H*), 10.28 (1H, s, C*H*O). NMR data are consistent published data.[159] Nitoalkene **226d** was then prepared using general procedure A. 3-Benzyloxy-2-bromo-4-methoxybenzaldehyde (1.38 g, 4.30 mmol) gave crude nitroalkene **226d** as a yellow solid. Purification by flash column chromatography (60% Et_2O/Pet. ether) yielded pure **226d** as a yellow solid (1.44 g, 92%); mp 110-112 °C (lit.[160] 107 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.95 (3H, s, OC*H*$_3$), 5.06 (2H, s, C*H*$_2$Ph), 6.94 (1H, d, *J* = 8.7, Ar*H*), 7.36-7.43 (4H, m, Ar*H*), 7.51 (1H, d, *J* = 13.6, C*H*Ar), 7.55 (2H, d, *J* = 6.8, Ar*H*), 8.42 (1H, d, *J* = 13.6, C*H*NO_2). NMR data are consistent published data.[160]

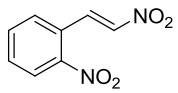
2-Chloro-3-((E)-2-nitrovinyl)pyridine (226e)



226e

Prepared using general procedure B. 2-Chloro-3-pyridine carboxaldehyde (200 mg, 1.41 mmol) gave crude nitroalkene **226e** as a brown solid. Purification by flash column chromatography (30% EtOAc/Pet. ether) yielded pure **226e** as a yellow solid (210 mg, 81%); mp 98-100 °C; R_f 0.39 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3084-2840 (C-H), 1633 (C=N), 1524 (N-O), 1509 (C=C), 1398, 1349 (N-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, ddd, *J* = 7.8, 4.8, 0.4, Ar*H*), 7.60 (1H, d, *J* = 13.8, C*H*Ar), 7.91 (1H, dd, *J* = 7.8, 1.9, Ar*H*), 8.33 (1H, d, *J* = 13.8, C*H*NO_2), 8.53 (1H, dd, *J* = 4.8, 1.9, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.1 (Ar*C*H), 125.7 (Ar*C*CH), 133.7 (*C*HNO_2), 137.1 (Ar*C*H), 140.2 (*C*HAr), 152.2 (Ar*C*NO_2), 152.2 (Ar*C*H); m/z (EI) 184 (7%, M^+), 149 (20%, M^+-Cl), 138 (15%, M^+-NO_2), 102 (100%, M^+-(Cl+NO2)); HRMS $C_7H_5ClN_2O_2$ calcd. 184.0034, found 184.0031; Anal. calcd. for $C_7H_5ClN_2O_2$: C, 45.55; H, 2.73; N, 15.18; found: C, 45.80; H, 2.72; N, 14.92%.

1-Nitro-2-((*E*)-2-nitro-vinyl)-benzene (325a)

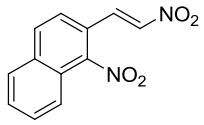


325a

Prepared using general procedure B. 2-Nitrobenzaldehyde (1.04 g, 6.86 mmol) afforded crude nitroalkene **325a** as a brown oil. Purification by filtration through a short plug of

silica (40% EtOAc/Pet. ether) followed by recrystallisation from EtOAc/Pet. ether yielded pure nitroalkene **325a** as a yellow solid (544 mg, 59%); mp 98-100 °C (Lit.[161a] 106-107 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 13.5, C*H*Ar), 7.61 (1H, dd, *J* = 7.7, 1.4, Ar*H*), 7.70 (1H, td, *J* = 7.8, 1.5, Ar*H*), 7.76 (1H, td, *J* = 7.6, 1.1, Ar*H*), 8.22 (1H, dd, *J* = 8.1, 1.3, Ar*H*), 8.55 (1H, d, *J* = 13.6, C*H*NO_2). ^{1}H NMR data are consistent with published data.[161b]

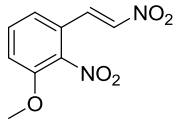
1-Nitro-2-((*E*)-2-nitrovinyl)naphthalene (325b)



325b

Prepared using general procedure B except with 30 equiv. $MeNO_2$. 1-Nitro-2-naphthaldehyde (513 mg, 2.55 mmol) afforded crude nitroalkene **325b** as a brown oil. Purification by filtration through a short plug of silica (100% EtOAc/Pet. ether) followed by recrystallisation from EtOAc/Pet. ether yielded pure **325b** as a brown solid (356 mg, 57%); mp 150-152 °C; R_f 0.36 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3105-2869 (C-H), 1635, 1511 (N-O), 1337 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (1H, d, *J* = 8.7, Ar*H*), 7.68 (1H, d, *J* = 13.5, C*H*Ar), 7.71-7.75 (2H, m, Ar*H*), 7.83-7.85 (1H, m, Ar*H*), 7.97-7.99 (1H, m, Ar*H*), 8.07 (1H, d, *J* = 8.7, Ar*H*), 8.10 (1H, d, *J* = 13.6, *C*HNO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 119.8 (Ar*C*CH), 122.2 (Ar*C*H), 122.8 (Ar*C*H), 124.5 (Ar*C*), 128.5 (Ar*C*H), 129.7 (Ar*C*H), 130.0 (Ar*C*H), 131.8 (*C*HNO_2), 131.9 (Ar*C*H), 135.3 (Ar*C*), 140.8 (*C*HAr), 149.4 (Ar*C*NO_2); m/z (EI) 244 (15%, M^+); HRMS $C_{12}H_8N_2O_4$ calcd. 244.0479, found 244.0481.

1-Methoxy-2-nitro-3-((*E*)-2-nitrovinyl)benzene (325c)

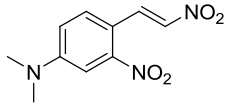


325c

Prepared using general procedure B except with 30 equiv. $MeNO_2$. 3-Methoxy-2-nitrobenzaldehyde (1.21 g, 6.70 mmol) afforded crude nitroalkene **325c** as a brown oil. Purification by filtration through a short plug of silica (100% EtOAc/Pet. ether) followed by recrystallisation from EtOAc/Pet. ether yielded pure **325c** as a brown solid (1.08 g, 72%); mp 140-142 °C; R_f 0.13 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3121-2849 (C-H),

1603, 1580 (N-O), 1519 (N-O), 1479, 1360 (N-O), 1341 (N-O), 1288 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.96 (3H, s, OCH_3), 7.21 (2H, d, *J* = 8.2, Ar*H*), 7.52 (1H, d, *J* = 13.7, C*H*Ar), 7.53 (1H, t, *J* = 8.2, Ar*H*), 7.88 (1H, d, *J* = 13.6, C*H*NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 56.9 (O*C*H_3), 115.7 (Ar*C*H), 119.3 (Ar*C*H), 124.0 (Ar*C*CH), 131.7 (*C*HNO_2), 131.9 (Ar*C*H), 140.6 (*C*HAr), 141.3 (Ar*C*NO_2), 151.7 (Ar*C*O); m/z (EI) 224 (100%, M^+), 178 (78%, M^+-NO_2); HRMS $C_9H_8N_2O_5$ calcd. 224.0428, found 224.0429.

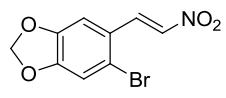
(*E*)-*N*,*N*-Dimethyl-3-nitro-4-(2-nitrovinyl)aniline (325d)



325d

Prepared using general procedure B except with 40 equiv. $MeNO_2$. 4-Dimethylamino-2-nitrobenzaldehyde (1.12 g, 5.77 mmol) afforded crude nitroalkene **325d** as a red solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **325d** as a red solid (896 mg, 65%); mp 175-177 °C; R_f 0.13 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3114-2826 (C-H), 1606, 1539 (N-O), 1500 (C=C), 1325 (N-O), 1282 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.14 (6H, s, N(CH_3)$_2$), 6.86 (1H, dd, *J* = 8.9, 2.7, Ar*H*), 7.24 (1H, d, *J* = 2.7, Ar*H*), 7.47 (1H, d, *J* = 13.4, C*H*Ar), 7.51 (1H, d, *J* = 8.9, Ar*H*), 8.41 (1H, d, *J* = 13.4, C*H*NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 40.3 (N(*C*H_3)$_2$), 107.5 (Ar*C*H), 110.9 (Ar*C*CH), 115.4 (Ar*C*H), 130.0 (Ar*C*H), 134.9 (*C*HNO_2), 136.2 (*C*HAr), 151.0 (Ar*C*NO_2), 152.4 (Ar*C*NMe_2); m/z (EI) 237 (100%, M^+), 160 (M^+- NO_2Me_2H); HRMS $C_{10}H_{11}N_3O_4$ calcd. 237.0744, found 237.0748.

5-Bromo-6-[(*E*)-2-nitrovinyl]-1,3-benzodioxole (348)



348

Prepared using general procedure A. 6-Bromopiperonal (1.10 g, 8.92 mmol) gave crude nitroalkene **348** as yellow solid. Purification by recrystallisation from toluene/pet. ether provided pure **348** as a yellow solid (1.20 mg, 68%); mp 161-163 °C (lit.[162] 154.5-155.5 °C); ^1H NMR (600 MHz, $CDCl_3$) δ 6.09 (2H, s, OCH_2O), 7.02 (1H, s, Ar*H*), 7.14 (1H, s, Ar*H*), 7.45 (1H, d, *J* = 13.5, C*H*NO_2), 8.38 (1H, d, *J* = 13.6, C*H*Ar). NMR data are consistent with the published data.[162]

4.4.2 Preparation of Nitroalkanes

General Procedure C

To a stirred solution of nitroalkene (1.00 mmol) in THF (5.00 mL) at 0 °C was added dropwise $LiHBEt_3$ (1M in THF, 1.20 mmol). After 30 min at 0 °C silica (0.50 g) was added and the mixture stirred for 10 min before being filtered. The filtrate was collected and the solvent removed *in vacuo* to leave crude nitroalkane which was purified by flash column chromatography.

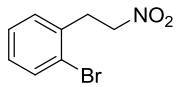
General Procedure D

To a suspension of nitroalkene (1.00 mmol) in MeOH (10.0 mL) at rt was added $NaBH_4$ (3.00 mmol) in one portion. The reaction was stirred at rt for 60 min to give a homogeneous solution. H_2O (10 mL) was added and the product was extracted into CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude nitroalkane which was purified by flash column chromatography.

General Procedure E

To a solution of nitroalkane (1.00 mmol) in MeOH (10.0 mL) at rt was added 10% Pd on carbon (10% by weight). The flask was triple evacuated/N_2 filled and then triple evacuated/H_2 filled. The reaction was stirred under H_2 with careful monitoring by TLC. The reaction reached completion after 30-60 min and was subsequently filtered through Celite®. Concentration of the filtrate *in vacuo* yielded the crude aniline which was purified by flash column chromatography or used without further purification.

2-Bromo(2-nitroethyl)benzene (223)

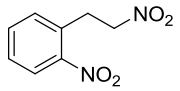


223

Prepared using general procedure C. Nitroalkene **226a** (300 mg, 1.32 mmol) gave crude nitroalkane **223** as a pale yellow oil. Purification by flash column chromatography (10% Et_2O/Pet. ether) afforded pure **223** as a colourless oil (245 mg, 81%); R_f 0.27 (10% Et_2O/Pet. ether); IR υ_{max} ($CHCl_3$) 3062-2923 (C-H), 1557 (N-O), 1474, 1432, 1380, 1347 (N-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (2H, t, J = 7.3, CH_2Ar), 4.66 (2H, t, J =

7.3, C*H*$_2$NO$_2$), 7.17 (1H, m, Ar*H*), 7.28 (2H, m, Ar*H*), 7.59 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 33.9 (*C*H$_2$Ar), 74.4 (*C*H$_2$NO$_2$), 124.3 (Ar*C*CH$_2$), 128.0 (Ar*C*H), 129.4 (Ar*C*H), 131.2 (Ar*C*H), 133.3 (Ar*C*H), 135.0 (Ar*C*Br); m/z (ESI$^+$) 252+254 (1:1, 100%, M+Na$^+$); HRMS $C_8H_8BrNO_2Na$ calcd. 251.9631, found 251.9645; Anal. calcd. for $C_8H_8BrNO_2$: C, 41.77; H, 3.51; N, 6.09; found: C, 41.95; H, 3.50; N, 5.92%.

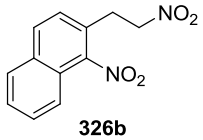
Nitro-2-(2-nitro-ethyl)-benzene (326)



326

Prepared using general procedure C. Nitroalkene **325a** gave crude nitroalkane **326** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) afforded pure **326** as a brown oil (581 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (2H, t, *J* = 6.8, C*H*$_2$Ar), 4.49 (2H, t, *J* = 6.8, C*H*$_2$NO$_2$), 7.41 (1H, dd, *J* = 7.7, 1.3, Ar*H*), 7.50 (1H, m, Ar*H*), 7.61 (1H, td, *J* = 7.5, 1.4, Ar*H*), 8.09 (1H, dd, *J* = 8.2, 1.3, Ar*H*). ^{1}H NMR data are consistent with the published data.[163]

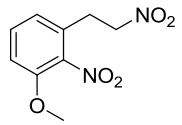
1-Nitro-2-(2-nitroethyl)naphthalene (326b)



326b

Prepared using general procedure D. Nitroalkene **325b** (211 mg, 0.864 mmol) gave crude nitroalkane **326b** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) afforded pure **326b** as a brown solid (135 mg, 63%); mp 91-93 °C; R_f 0.46 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3073-2868 (C-H), 1548 (N-O), 1517 (N-O), 1381 (N-O), 1349 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.48 (2H, t, *J* = 7.2, C*H*$_2$Ar), 4.76 (2H, t, *J* = 7.2, C*H*$_2$NO$_2$), 7.41 (1H, d, *J* = 8.5, Ar*H*), 7.63 (1H, td, *J* = 7.5, 0.8, Ar*H*), 7.68 (1H, td, *J* = 7.7, 1.1, Ar*H*), 7.78 (1H, d, *J* = 8.5, Ar*H*), 7.93 (1H, d, *J* = 8.2, Ar*H*), 7.99 (1H, d, *J* = 8.5, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.9 (*C*H$_2$Ar), 75.1 (*C*H$_2$NO$_2$), 121.8 (Ar*C*H), 124.7 (Ar*C*CH$_2$), 125.5 (Ar*C*), 126.7 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 129.3 (Ar*C*H), 131.8 (Ar*C*H), 133.3 (Ar*C*), 148.3 (Ar*C*NO$_2$); m/z (EI) 246 (27%, M$^+$); HRMS $C_{12}H_{10}N_2O_4$ calcd. 246.0635, found 246.0638.

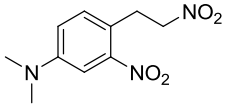
1-Methoxy-2-nitro-3-(2-nitroethyl)benzene (336)



336

Prepared using general procedure D. Nitroalkene **325c** (120 mg, 0.535 mmol) gave crude nitroalkane **336** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) afforded pure **336** as a colourless oil (83 mg, 67%); R_f 0.21 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3095-2761 (C-H), 1559 (N-O), 1535, 1520 (N-O), 1477, 1459, 1437, 1384 (N-O), 1364 (N-O), 1295, 1274 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.27 (2H, t, *J* = 7.1, C*H*$_2$Ar), 3.91 (3H, s, OC*H*$_3$), 4.64 (2H, t, *J* = 7.1, C*H*$_2$NO$_2$), 6.89 (1H, d, *J* = 7.7, Ar*H*), 7.01 (1H, d, *J* = 8.5, Ar*H*), 7.40 (1H, t, *J* = 8.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.0 (*C*H$_2$Ar), 56.6 (O*C*H$_3$), 75.0 (*C*H$_2$NO$_2$), 112.2 (Ar*C*H), 122.0 (Ar*C*H), 129.0 (Ar*C*CH$_2$), 131.8 (Ar*C*H), 141.7 (Ar*C*NO$_2$), 151.4 (Ar*C*O); m/z (EI) 226 (8%, M^+), 151 (24%, M^+-$C_2H_5NO_2$); HRMS $C_9H_{10}N_2O_5$ calcd. 226.0584, found 226.0581.

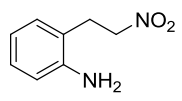
***N*,*N*-Dimethyl-3-nitro-4-(2-nitroethyl)aniline (337)**



337

Prepared using general procedure D. Nitroalkene **325d** (175 mg, 0.738 mmol) gave crude nitroalkane **337** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) afforded pure **337** as an orange oil (115 mg, 65%); mp 72-73 °C; R_f 0.45 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3106-2816 (C-H), 1625, 1548 (N-O), 1528 (N-O), 1444, 1363 (N-O), 1345 (N-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.02 (6H, s, N(C*H*$_3$)$_2$), 3.47 (2H, t, *J* = 6.8, ArC*H*$_2$),4.71 (2H, t, *J* = 6.8, C*H*$_2$NO$_2$), 6.85 (1H, dd, *J* = 8.5, 2.8, Ar*H*), 7.17 (1H, d, *J* = 8.5, Ar*H*), 7.30 (1H, d, *J* = 2.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 30.5 (Ar*C*H$_2$), 39.9 (N(*C*H$_3$)$_2$), 75.5 (*C*H$_2$NO$_2$), 107.5 (Ar*C*H), 116.6 Ar*C*H), 116.8 (Ar*C*CH$_2$), 132.9 (Ar*C*H), 149.2 (Ar*C*), 149.9 (Ar*C*); m/z (EI) 239 (100%, M^+); HRMS $C_{10}H_{13}N_3O_4$ calcd. 239.0901, found 239.0905.

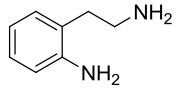
2-Amino-(2-nitro-ethyl)-benzene (317)



317

Prepared using general procedure E. Nitroalkene **326** (87 mg, 0.44 mmol) gave aniline **317** as a brown oil (78 mg, 100%) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (2H, t, *J* = 7.6, C*H*$_2$Ar), 3.71 (2H, br s, N*H*$_2$), 4.64 (2H, t, *J* = 7.6, C*H*$_2$NO$_2$), 6.72 (1H, dd, *J* = 8.0, 1.2, Ar*H*), 6.78 (1H, td, *J* = 7.5, 1.3, Ar*H*), 7.04 (1H, dd, *J* = 7.6, 1.3, Ar*H*), 7.12 (1H, td, *J* = 7.7, 1.5, Ar*H*). NMR data are consistent with the published data.[163]

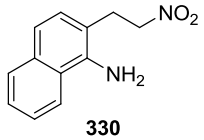
2-Amino-1-(2-amino-ethyl)-benzene (327)



327

Prepared using general procedure E except with stirring under H_2 for 18 h. Nitroalkene **326** (121 mg, 0.617 mmol) gave pure aniline **327** as a pale brown oil (84 mg, 100%); ^{1}H NMR (400 MHz, CD_3OD) δ 2.69 (2H, t, *J* = 7.4, C*H*$_2$Ar), 2.87 (2H, t, *J* = 7.4, C*H*$_2$NH$_2$), 6.65 (1H, td, *J* = 7.4, 1.1, Ar*H*), 6.73 (1H, dd, *J* = 8.4, 1.1, Ar*H*), 6.98 (2H, m, Ar*H*). NMR data are consistent with the published data.[164]

1-Amino-2-(2-nitroethyl)naphthalene (330)



330

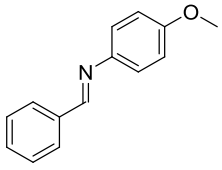
Prepared using general procedure E. Nitroalkene **326b** (106 mg, 0.431 mmol) gave crude aniline **330** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) afforded pure **330** as a brown oil (42 mg, 45%); R_f 0.28 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3467 (N-H), 3394 (N-H), 3057-2917 (C-H), 1629, 1545 (N-O), 1402, 1379 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.42 (2H, t, *J* = 7.7, C*H*$_2$Ar), 4.30 (2H, br s, N*H*$_2$), 3.68 (2H, t, *J* = 7.7, C*H*$_2$NO$_2$), 7.18 (1H, d, *J* = 8.3, Ar*H*), 7.31 (1H, d, *J* = 8.3, Ar*H*), 7.46-7.51 (2H, m, Ar*H*), 7.79-7.80 (1H, m, Ar*H*), 7.82 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 30.0 (*C*H$_2$Ar), 74.2 (*C*H$_2$NO$_2$), 113.6 (Ar*C*CH$_2$), 119.3 (Ar*C*H), 120.6 (Ar*C*H), 123.7 (Ar*C*), 125.6 (Ar*C*H), 126.0 (Ar*C*H), 128.0 (Ar*C*H), 128.7 (Ar*C*H), 133.8 (Ar*C*), 139.7 (Ar*C*NH$_2$); m/z (EI) 216 (100%, M$^+$), 170 (89%, M$^+$-NO$_2$), 169 (100%, M$^+$-NO$_2$H); HRMS $C_{12}H_{12}N_2O_2$ calcd. 216.0893, found 216.0897.

4.4.3 Preparation of Imines

General Procedure F

To a solution of *p*-anisidine (1.00 mmol) in DCM (5.00 mL) was added basic Al_2O_3 (0.50 g). To the vigorously stirred brown suspension was added aldehyde (1.00 mmol). The mixture was stirred at room temperature for 1-18 h before being filtered through Celite®. The filtrate was concentrated *in vacuo* to yield crude imine, which was either used without further purification or recrystallised from EtOAc/Pet. ether.

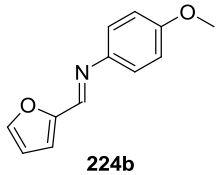
(4-Methoxyphenyl)[1-phenylmeth-(E)-ylidene]amine (224a)



224a

Prepared using general procedure F. Benzaldehyde (34.8 g, 283 mmol) gave crude imine **224a** as a yellow solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **224a** as a pale yellow solid (56.2 g, 94%); mp 70-72 °C (lit.[165] 70-71 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (3H, s, OC*H*$_3$), 6.95 (2H, m, Ar*H*), 7.25 (2H, m, Ar*H*), 7.48 (3H, m, Ar*H*), 7.90 (2H, m, Ar*H*), 8.50 (1H, s, C*H*N). NMR data are consistent with the published data.[165]

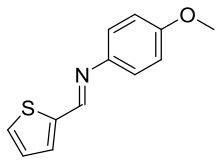
Furan-2-ylmeth-(E)-ylidene(4-methoxyphenyl)amine (224b)



224b

Prepared using general procedure F. 2-Furaldehyde (2.02 mL, 24.4 mmol) gave crude imine **224b** as a brown oily solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **224b** as a yellow solid (3.17 g, 65%); mp 65-66 °C (lit.[53] 66-68 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (3H, s, OC*H*$_3$), 6.56 (1H, dd, *J* = 3.4, 1.8, furyl-4-*H*), 6.92 (1H, m, furyl-3-*H*), 6.93 (2H, m, Ar*H*), 7.27 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 1.7, furyl-5-*H*), 8.32 (1H, s, C*H*N). NMR data are consistent with the published data.[53]

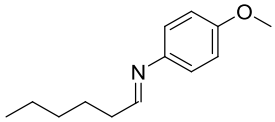
Thiophen-2-ylmeth-(E)-ylidene(4-methoxyphenyl)amine (224c)



224c

Prepared using general procedure F. 2-Thiophene carboxaldehyde (730 mg, 5.93 mmol) gave crude imine **224c** as a yellow solid. Purification by recrystallisation from pet. ether yielded pure **224c** as a yellow solid (916 mg, 71%); mp 48-49 °C (lit.[166] 47.5-48.0 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84 (3H, s, OC*H3*), 6.93 (2H, dm, *J* = 9.0, Ar*H*), 7.13 (1H, dd, *J* = 5.0, 3.6, thiophenyl-4-*H*), 7.24 (2H, dm, *J* = 9.0, Ar*H*), 7.46 (1H, dd, *J* = 3.5, 0.9, thiophenyl-3-*H*), 7.49 (1H, d, *J* = 5.0, thiophenyl-5-*H*), 8.60 (1H, s, C*H*N). NMR data are consistent with the published data.[166]

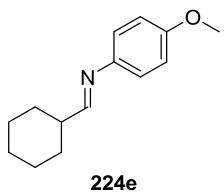
Hex-(E)-ylidene(4-methoxyphenyl)amine (224d)



224d

To a vigorously stirred suspension of *p*-anisidine (308 mg, 2.50 mmol) and 4 Å MS in DCM (13 mL) at -78 °C was added *n*-hexanal (300 μL, 2.50 mL). The reaction was stirred at -78 °C for 2 h before being removed form the cold bath and filtered through Celite®. The solvent was removed *in vacuo* to give imine **224d** as a brown oil (411 mg, 80%, 85% pure) which was used immediately without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 6.9, CH_2CH_3), 1.19-1.30 (4H, m, $(CH_2)_2CH_3$), 2.25 (2H, quintet, *J* = 7.4, CH_2CH_2CHN), 3.32 (3H, s, OCH_3), 6.80 (2H, m, Ar*H*), 7.10 (2H, m, Ar*H*), 7.63 (1H, d, *J* = 4.6, C*H*N). NMR data are consistent with the published data.[53]

Cyclohexylmeth-(E)-ylidene(4-methoxyphenyl)amine (224e)

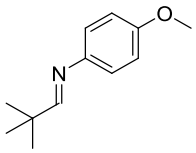


224e

Prepared using general procedure F. Cyclohexane carboxaldehyde (300 μL, 2.44 mmol) gave imine **224e** as a pale yellow oil (504 mg, 95%) which was used without further

purification and stored at -20 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.42 (5H, m, Cy*H*), 1.69-1.96 (5H, m, Cy*H*), 2.37 (1H, m, Cy*H*), 3.81 (3H, s, OCH_3), 6.87 (2H, m, Ar*H*), 7.03 (2H, m, Ar*H*), 7.72 (1H, d, *J* = 5.2, C*H*N). NMR data are consistent with the published data.[53]

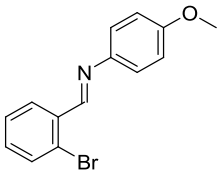
2,2-Dimethylprop-(*E*)-ylidene(4-methoxyphenyl)amine (224f)



224f

Prepared using general procedure F except with 2.0 equiv. of aldehyde with respect to aniline. Trimethylacetaldehyde (1.44 g, 16.7 mmol) and *p*-anisidine (1.03 g, 8.36 mmol) gave imine **224f** as a colourless solid (1.60 g, 100%) which was used without further purification; mp 50-52 °C (lit.[167] 50-52 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (9H, s, C(CH_3)$_3$), 3.81 (3H, s, OCH_3), 6.87 (2H, m, Ar*H*), 7.01 (2H, m, Ar*H*), 7.71 (1H, m, C*H*N). NMR data are consistent with the published data.[167]

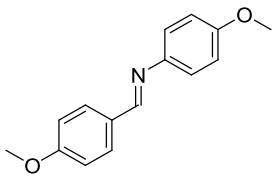
[1-(2-Bromophenyl)meth-(E)-ylidene](4-methoxyphenyl)amine (224g)



224g

Prepared using general procedure F. 2-Bromobenzaldehyde (1.28 mL, 11.0 mmol) gave crude imine **224g** as a yellow oily solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **224g** as a yellow solid (2.47 g, 77%); mp 61-64 °C (lit.[168] 73-74 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (3H, s, OCH_3), 6.96 (2H, dm, *J* = 9.0, Ar*H*), 7.29 (2H, dm, *J* = 9.0, Ar*H*), 7.31 (1H, td, *J* = 7.9, 1.9, Ar*H*), 7.41 (1H, m, Ar*H*), 7.62 (1H, dd, *J* = 8.0, 1.1, Ar*H*), 8.23 (1H, dd, *J* = 7.8, 1.7, Ar*H*), 8.88 (1H, m, C*H*N). NMR data are consistent with the published data.[168]

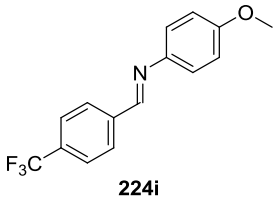
[1-(4-Methoxyphenyl)meth-(E)-ylidene]-(4-methoxyphenyl)amine (224h)



224h

Prepared using general procedure F. 4-Methoxybenzaldehyde (1.52 g, 12.5 mmol) gave crude imine **224h** as a pale yellow solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **224h** as a white solid (2.70 g, 90%); mp 144-145 °C (lit.[169] 144 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.84 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 6.94 (2H, dm, Ar*H*), 6.99 (2H, dm, Ar*H*), 7.22 (2H, dm, Ar*H*), 7.85 (2H, dm, Ar*H*), 8.42 (1H, s, C*H*N). NMR data are consistent with the published data.[169]

[1-(4-Trifluoromethylphenyl)meth-(E)-ylidene]-(4-methoxyphenyl)amine (224i)



224i

Prepared using general procedure F. 4-Trifluoromethylbenzaldehyde (1.50 mL, 11.0 mmol) gave crude imine **224i** as a yellow solid. Purification by recrystallisation from EtOAc/Pet. ether yielded pure **224i** as a white solid (2.52 g, 82%); mp 123-125 °C (Lit.[170] 126-127 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (3H, s, OC*H*$_3$), 6.96 (2H, dm, *J* = 9.0, Ar*H*), 7.29 (2H, dm, *J* = 9.0, Ar*H*), 7.72 (2H, d, *J* = 8.2, Ar*H*), 8.01 (2H, d, *J* = 8.1, Ar*H*), 8.53 (1H, s, C*H*N). NMR data are consistent with the published data.[170]

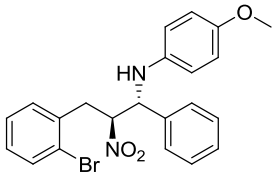
4.4.4 Preparation of *β*-Nitroamines

General Procedure G

To a solution of nitroalkene (1.00 mmol) in CH_2Cl_2 (5.0 mL) at room temperature was added dropwise lithium triethylborohydride (1.0 M in THF, 1.05 mmol). The mixture was stirred at room temperature for 20 min to give a white precipitate before being cooled to -78 °C. A solution of imine (1.10 mmol) in CH_2Cl_2 (2.8 mL) was added and the mixture stirred for 10 min before the dropwise addition of trifluoroacetic acid (1.15 mmol) over 30 s. The

reaction was stirred at -78 °C for 90 min before being removed from the cold bath and allowed to warm for 5 min giving a yellow solution. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (15 mL) and the product extracted into Et_2O (2 x 20 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude *β*-nitroamine which was used without further purification.

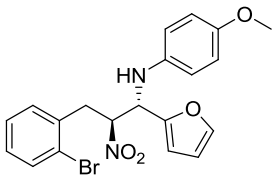
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230a)



230a

Prepared using general procedure G. Nitroalkene **226a** (299 mg, 1.31 mmol) and imine **224a** (305 mg, 1.44 mmol) afforded crude *β*-nitroamine **230a** as a yellow solid (812 mg, 98% conv., *anti*:*syn* >20:1); R_f 0.34 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3393 (N-H), 3058-2833 (C-H), 1552 (N-O), 1511 (C=C), 1243 (C-O, N-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (1H, dd, *J* = 14.7, 10.9, C*H*$_2$), 3.55 (1H, dd, *J* = 14.7, 2.8, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 4.26 (1H, d, *J* = 6.8, N*H*), 4.93 (1H, t, *J* = 6.4, C*H*Ph), 5.19 (1H, ddd, *J* = 10.9, 5.9, 2.9, C*H*NO_2), 6.60 (2H, dm, *J* = 8.9, Ar*H*), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 7.10-7.26 (3H, m, Ar*H*), 7.32-7.42 (5H, m, Ar*H*), 7.53 (1H, dd, *J* = 7.9, 0.9, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.7 (*C*H_2), 55.7 (O*C*H_3), 62.1 (*C*HPh), 91.7 (*C*HNO_2), 114.8 (Ar*C*H), 115.9 (Ar*C*H), 124.3 (Ar*C*CH_2), 127.1 (Ar*C*H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*H), 129.3 (Ar*C*H), 131.6 (Ar*C*H), 133.2 (Ar*C*H), 135.0 (Ar*C*Br), 137.4 (Ar*C*CHNH), 139.9 (Ar*C*N), 153.1 (Ar*C*O); m/z (ESI^+) 441+443 (1:1, 42%, $M+H^+$), 212 (67%, $PhCH^+NHPMP$); HRMS $C_{22}H_{22}(^{79}Br)N_2O_3$ calcd. 441.0808, found 441.0798.

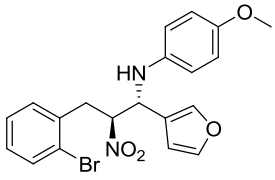
_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-1-(furan-2-yl)-2-nitropropyl)-4-methoxyaniline (230b)



230b

Prepared using general procedure G. Nitroalkene **226a** (1.01 g, 4.42 mmol) and imine **224b** (978 mg, 4.86 mmol) afforded crude *β*-nitroamine **230b** as a yellow oily solid (2.59 g, 96% conv., *anti*:*syn* = 7:1); R_f^{anti} 0.25 (20% Et_2O/Pet. ether); R_f^{syn} 0.20 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3368 (N-H), 3124-2834 (C-H), 1551 (N-O), 1510 (C=C), 1240 (C-O, N-O), 1034 (C-O) cm^{-1}; ^1H NMR^{anti} (400 MHz, $CDCl_3$) δ 3.47 (1H, dd, *J* = 14.7, 10.0, C*H*$_2$), 3.64 (1H, dd, *J* = 14.6, 3.9, C*H*$_2$), 3.75 (3H, s, OC*H*$_3$), 4.16 (1H, br d, *J* = 9.6, N*H*), 5.02 (1H, dd, *J* = 9.9, 6.1, C*H*Furyl), 5.25 (1H, ddd, *J* = 10.0, 6.1, 4.0, C*H*NO_2), 6.30-6.34 (2H, m, Furyl-3,4-*H*), 6.64-6.68 (2H, m, Ar*H*), 6.75-6.80 (2H, m, Ar*H*), 7.12-7.27 (3H, m, Ar*H*), 7.41 (1H, m, Furyl-5-*H*), 7.57 (1H, m, Ar*H*); ^1H NMR^{syn} (400 MHz, $CDCl_3$) δ 3.30 (1H, dd, *J* = 14.3, 4.7, C*H*$_2$), 3.41 (1H, dd, *J* = 14.3, 9.6, C*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 4.16 (1H, br d, *J* = 9.6, N*H*), 4.90 (1H, dd, *J* = 10.7, 7.9, C*H*Furyl), 5.33 (1H, ddd, *J* = 9.6, 7.9, 4.8, C*H*NO_2), 6.30-6.34 (2H, m, Furyl-3,4-*H*), 6.64-6.68 (2H, m, Ar*H*), 6.75-6.80 (2H, m, Ar*H*), 7.12-7.27 (3H, m, Ar*H*), 7.41 (1H, m, Furyl-5-*H*), 7.55 (1H, m, Ar*H*); ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 36.4 (*C*H_2), 55.8 (O*C*H_3), 56.5 (*C*HFuryl), 89.3 (*C*HNO_2), 108.9 (Furyl-3-*C*H), 110.7 (Furyl-4-*C*H), 115.0 (Ar*C*H), 116.4 (Ar*C*H), 124.5 (Ar*C*CH_2), 128.1 (Ar*C*H), 129.5 (Ar*C*H), 131.8 (Ar*C*H), 133.3 (Ar*C*H), 135.1 (Ar*C*Br), 139.6 (Ar*C*N), 143.0 (Furyl-5-*C*H), 150.1 (Furyl-2-*C*), 153.6 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 37.5 (*C*H_2), 55.7 (O*C*H_3), 56.4 (*C*HFuryl), 90.0 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 430+432 (1:1, 5% M^+), 202 (96%, FurylCH^+NHPMP); HRMS $C_{20}H_{19}(^{79}Br)N_2O_4$ calcd. 430.0523, found 430.0531.

N-((1*R**,2*S**)-3-(2-Bromophenyl)-1-(furan-3-yl)-2-nitropropyl)-4-methoxyaniline (230c)

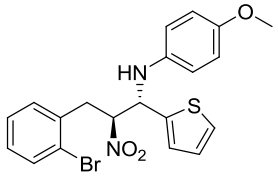


230c

Prepared using general procedure G. Nitroalkene **226a** (1.29 g, 5.65 mmol) and 3-furyl-imine (1.25 g, 6.22 mmol) afforded crude *β*-nitroamine **230c** as a yellow oily solid (3.20 g, >99% conv., *anti*:*syn* = 7:1); IR υ_{max} (neat) 3392 (N-H), 3131-2834 (C-H), 1551 (N-O), 1510 (C=C), 1241 (C-O, N-O), 1025 (C-O) cm^{-1}; ^1H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.43 (1H, dd, *J* = 14.6, 10.3, C*H*$_2$), 3.59 (1H, dd, *J* = 14.6, 3.5, C*H*$_2$), 3.76 (3H, s, OC*H*$_3$), 4.00 (1H, br s, N*H*), 4.91 (1H, d, *J* = 4.5, C*H*NH), 5.16 (1H, ddd, *J* = 10.2, 6.3, 3.8, C*H*NO_2),

6.41 (1H, m, Furyl-4-*H*), 6.66 (2H, dm, *J* = 8.9, Ar*H*), 6.79 (2H, dm, *J* = 8.9, Ar*H*), 7.16 (1H, td, *J* = 7.6, 1.8, Ar*H*), 7.20 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.25 (1H, td, *J* = 7.5, 1.0, Ar*H*), 7.42 (1H, m, Furyl-5-*H*), 7.47 (1H, s, Furyl-2-*H*), 7.57 (1H, dd, *J* = 8.0, 0.9, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ .35 (1H, dd, *J* = 14.3, 9.7, CH_2), 3.39 (1H, dd, *J* = 14.4, 5.0, CH_2), 3.75 (3H, s, OCH_3), 4.06 (1H, br s, N*H*), 4.81 (1H, br m, C*H*NH), 5.22 (1H, ddd, *J* = 9.6, 7.3, 5.0, C*H*NO_2), the remaining signals could not be determined;^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 36.7 (*C*H_2), 54.7 (*C*HNH), 55.8 (O*C*H_3), 90.3 (*C*HNO_2), 108.6 (Furyl-4-*C*H), 115.0 (Ar*C*H), 116.3 (Ar*C*H), 122.2 (Furyl-3-*C*), 124.5 (Ar*C*CH_2), 128.1 (Ar*C*H), 129.5 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.0 (Ar*C*Br), 139.7 (Ar*C*N), 140.8 (Furyl-2-*C*H), 144.1 (Furyl-5-*C*H), 153.5 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 37.7 (*C*H_2), 54.3 (*C*HNH), 55.7 (O*C*H_3), 91.1 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 432+430 (1:1, 25%, M^+), 202 (98%, FurylCH^+NHPMP); HRMS $C_{20}H_{19}(^{79}Br)N_2O_4$ calcd. 430.0523, found 430.0518.

_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(thiophen-2-yl)propyl)-4-methoxyaniline (230d)

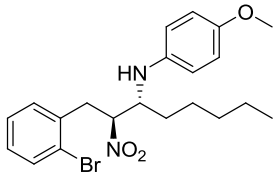


230d

Prepared using general procedure G. Nitroalkene **226a** (85 mg, 0.37 mmol) and 2-thiophenyl-imine **224c** (89 mg, 0.41 mmol) afforded crude *β*-nitroamine **230d** as a yellow solid (173 mg, 96% conv., *anti*:*syn* = 9:1); IR υ_{max} (neat) 3387 (N-H), 3069-2833 (C-H), 1551 (N-O), 1509 (C=C), 1241 (C-O and N-O), 1026 (C-O) cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.48 (1H, m, CH_2), 3.67 (1H, dd, *J* = 14.7, 2.7, CH_2), 3.74 (3H, s, OCH_3), 4.17 (1H, br d, *J* = 7.4, N*H*), 5.18-5.22 (2H, m, C*H*NO_2 + C*H*NH), 6.66 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 8.9, Ar*H*), 6.99 (1H, dd, *J* = 5.0, 3.6, thiophenyl-4-*H*), 7.07 (1H, d, *J* = 3.5, thiophenyl-3-*H*), 7.15 (1H, td, *J* = 7.6, 1.9, Ar*H*), 7.20 (1H, dd, *J* = 7.6, 1.8, Ar*H*), 7.25 (1H, td, *J* = 7.4, 1.1, Ar*H*), 7.27 (1H, m, thiophenyl-5-*H*), 7.56 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 3.35 (1H, m, CH_2), 3.73 (3H, s, OCH_3), 5.08 (1H, dd, *J* = 9.7, 7.8, C*H*NH), 5.26 (1H, ddd, *J* = 8.9, 7.8, 5.6, C*H*NO_2), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 36.5 (*C*H_2), 55.7 (O*C*H_3), 58.2 (*C*HNH), 91.6 (*C*HNO_2), 115.0 (Ar*C*H), 116.2 (Ar*C*H), 124.5 (Ar*C*CH_2), 125.7 (thiophenyl-5-*C*H),

125.9 (thiophenyl-3-*C*H), 127.5 (thiophenyl-4-*C*H), 128.1 (Ar*C*H), 129.6 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 134.9 (Ar*C*Br), 139.6 (Ar*C*N), 141.5 (thiophenyl-2-*C*), 153.6 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 38.0 (*C*H_2), 55.7 (O*C*H_3), 58.0 (*C*HNH), 92.0 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 448+446 (1:1, 20%, M^+), 217 (96%, thiophenylCH^+NHPMP); HRMS $C_{20}H_{19}(^{79}Br)N_2O_3S$ calcd. 446.0294, found 446.0310.

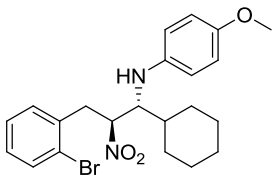
_N_-((2_S_*,3_R_*)-1-(2-Bromophenyl)-2-nitrooctan-3-yl)-4-methoxyaniline (230e)



230e

Prepared using general procedure G. Nitroalkene **226a** (968 mg, 4.24 mmol) and *n*-pentyl-imine **224d** (959 mg, 4.67 mmol) afforded crude *β*-nitroamine **230e** as a yellow oil (2.73 g, >95% conv., *anti*:*syn* = 17.5:1); IR υ_{max} (neat) 3379 (N-H), 3060-2834 (C-H), 1546 (N-O), 1509 (C=C), 1466, 1441, 1234 (N-O, C-O), 1036, 1025 (C-O) cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 6.9, C*H*$_3$CH$_2$), 1.29-1.44 (6H, m, *n*-Pentyl*H*), 1.61 (1H, m, *n*-Pentyl*H*), 1.81 (1H, m, *n*-Pentyl*H*), 3.39 (1H, dd, *J* = 14.5, 5.0, C*H*$_2$Ar), 3.45 (1H, dd, *J* = 14.4, 9.2, C*H*$_2$Ar), 3.76 (3H, s, OC*H*$_3$), 3.78 (1H, m, C*H*NH), 4.96 (1H, dt, *J* = 9.2, 4.7, C*H*NO_2), 6.53 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 8.9, Ar*H*), 7.15 (1H, td, *J* = 7.6, 1.6, Ar*H*), 7.21 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.25 (1H, td, *J* = 7.3, 1.0, Ar*H*), 7.57 (1H, dd, *J* = 8.0, 0.9, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 3.27 (1H, dd, *J* = 14.3, 5.1, C*H*$_2$Ar), 3.73 (3H, s, OC*H*$_3$), 5.13 (1H, dt, *J* = 9.9, 4.4, C*H*NO_2), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 14.2 (*C*H_3CH$_2$), 22.6 (*C*H_2CH$_3$), 26.1 (*C*H_2CH$_2$CH$_3$), 30.9 (*C*H_2CH$_2$CHN), 31.7 (*C*H_2CHN), 36.4 (*C*H_2Ar), 55.8 (O*C*H_3), 57.4 (*C*HNH), 89.4 (*C*HNO_2), 115.1 (Ar*C*H), 115.5 (Ar*C*H), 124.6 (Ar*C*CH_2), 128.0 (Ar*C*H), 129.4 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.4 (Ar*C*Br), 140.4 (Ar*C*N), 152.9 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 55.6 (O*C*H_3), 56.9 (*C*HNH), 89.7 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 436+434 (1:1, 10%, M^+), 206 (100%, $CH_3(CH_2)_4CH^+$NHPMP); HRMS $C_{21}H_{28}(^{79}Br)N_2O_3$ calcd. 434.1200, found 434.1204.

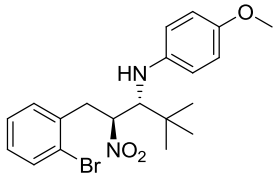
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-cyclohexyl-2-nitropropyl)-4-methoxyaniline (230f)



230f

Prepared using general procedure G. Nitroalkene **226a** (103 mg, 0.452 mmol) and cyclohexyl-imine **224e** (108 mg, 0.497 mmol) afforded crude *β*-nitroamine **230f** as a yellow solid (250 mg, 96% conv., *anti*:*syn* = 3.5:1); R_f^{anti} 0.23 (10% Et_2O/Pet. ether); R_f^{syn} 0.28 (10% Et_2O/Pet. ether); IR υ_{max} (neat) 3408 (N-H), 3062-2853 (C-H), 1547 (N-O), 1510 (C=C), 1241 (C-O, N-O), 1027 (C-O) cm^{-1}; ^1H NMR^{anti} (600 MHz, $CDCl_3$) δ 1.08-1.29 (4H, m, CyCH_2), 1.33 (1H, qd, *J* = 12.3, 3.1, CyCH_2), 1.53 (1H, m, CyC*H*), 1.64-1.85 (5H, m, CyH_2), 3.25 (1H, dd, *J* = 14.6, 11.2, CH_2Ar), 3.42 (1H, d, *J* = 10.5, N*H*), 3.55 (1H, dd, *J* = 14.6, 2.8, CH_2Ar), 3.76 (3H, s, OCH_3), 3.84 (1H, m, C*H*NH), 4.96 (1H, ddd, *J* = 11.2, 8.4, 2.8, C*H*NO_2), 6.68 (2H, m, Ar*H*), 6.80 (2H, m, Ar*H*), 7.12 (2H, m, Ar*H*), 7.21 (1H, td, *J* = 7.4, 1.1, Ar*H*), 7.54 (1H, d, *J* = 8.0, Ar*H*); ^1H NMR^{syn} (600 MHz, $CDCl_3$) δ 1.04-1.37 (5H, m, Cy), 1.52-1.94 (5H, m, Cy), 3.32 (1H, dd, *J* = 14.3, 4.0, CH_2Ar), 3.41 (1H, dd, *J* = 14.3, 10.1, CH_2Ar), 3.61 (1H, m, C*H*NH), 3.76 (3H, s, OCH_3), 3.84 (1H, d, *J* = 10.9, N*H*), 5.22 (1H, ddd, *J* = 10.0, 5.6, 4.3, C*H*NO_2), 6.62 (2H, m, Ar*H*), 6.78 (2H, m, Ar*H*), 7.08 (1H, dd, *J* = 7.5, 1.7, Ar*H*), 7.13-7.20 (2H, m, Ar*H*), 7.57 (1H, m, Ar*H*); ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 26.0 (Cy*C*H_2), 26.2 (Cy*C*H_2), 26.3 (Cy*C*H_2), 26.4 (Cy*C*H_2), 31.3 (Cy*C*H_2), 37.4 (*C*H_2Ar), 40.2 (Cy*C*H), 55.9 (O*C*H_3), 62.2 (*C*HNH), 89.9 (C*H*NO_2), 114.6 (Ar*C*H), 115.2 (Ar*C*H), 124.2 (Ar*C*), 128.1 (Ar*C*H), 129.3 (Ar*C*H), 131.5 (Ar*C*H), 133.2 (Ar*C*H), 135.5 (Ar*C*), 142.1 (Ar*C*), 152.6 (Ar*C*H); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 26.1 (Cy*C*H_2), 26.1 (Cy*C*H_2), 26.2 (Cy*C*H_2), 28.9 (Cy*C*H_2), 30.9 (Cy*C*H_2), 38.5 (*C*H_2Ar), 41.5 (Cy*C*H), 55.9 (O*C*H_3), 61.7 (*C*HNH), 89.4 (C*H*NO_2), 114.2 (Ar*C*H), 115.1 (Ar*C*H), 124.4 (Ar*C*), 128.1 (Ar*C*H), 129.5 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.1 (Ar*C*), 142.4 (Ar*C*), 152.2 (Ar*C*H); m/z (EI) 446+448 (1:1, 11%, M^+), 317+319 (1:1, 31%, M-(Cy+NO_2)), 218 (100%, $CyCH^+NHPMP$); HRMS $C_{22}H_{27}(^{79}Br)N_2O_3$ calcd. 446.1200, found 446.1200.

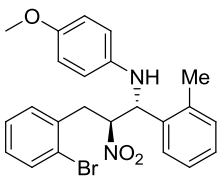
_N_-((2_S_*,3_R_*)-1-(2-Bromophenyl)-4,4-dimethyl-2-nitropentan-3-yl)-4-methoxyaniline (230g)



230g

Prepared using general procedure G. Nitroalkene **226a** (1.03 g, 4.52 mmol) and *t*-butyl-imine **224f** (950 mg, 4.97 mmol) afforded crude *β*-nitroamine **230g** as a yellow oil (2.20 g, 92% conv., *anti*:*syn* = 5.3:1); IR υ_{max} (neat) 3415 (N-H), 3060-2833 (C-H), 1548 (N-O), 1509 (C=C), 1471, 1232 (C-O), 1036, 1024 cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 1.07 (9H, s, $C(CH_3)_3$), 3.18 (1H, dd, *J* = 14.3, 12.0, CH_2), 3.56 (1H, dd, *J* = 14.5, 3.0, CH_2), 3.56 (1H, m, N*H*), 3.78 (3H, s, OCH_3), 3.90 (1H, dd, *J* = 8.6, 6.5, C*H*NH), 5.12 (1H, ddd, *J* = 11.6, 6.3, 3.2, $CHNO_2$), 6.78 (2H, dm, *J* = 8.9, Ar*H*), 6.84 (2H, dm, *J* = 8.9, Ar*H*), 7.06 (1H, dd, *J* = 7.5, 1.3. Ar*H*), 7.13 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.20 (1H, td, *J* = 7.5, 1.0, Ar*H*), 7.55 (1H, dd, *J* = 7.9, 0.7, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 1.04 (9H, s, $C(CH_3)_3$), 3.14 (1H, dd, *J* = 14.4, 3.7, CH_2), 3.38 (1H, dd, *J* = 14.4, 10.3, CH_2), 3.43 (1H, d, *J* = 10.5, C*H*NH), 4.51 (1H, d, *J* = 10.7, N*H*), 5.38 (1H, m, $CHNO_2$), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 26.7 ($C(CH_3)_3$), 37.5 ($C(CH_3)_3$), 38.7 (CH_2), 55.9 (OCH_3), 65.7 (*C*HNH), 90.2 ($CHNO_2$), 114.0 (Ar*C*H), 115.3 (Ar*C*H), 124.1 (Ar*C*CH_2), 128.0 (Ar*C*H), 129.3 (Ar*C*H), 131.7 (Ar*C*H), 133.1 (Ar*C*H), 135.5 (Ar*C*Br), 142.6 (Ar*C*N), 152.4 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 27.1 ($C(CH_3)_3$), 37.3 ($C(CH_3)_3$), 40.4 (CH_2), 55.6 (OCH_3), 65.2 (*C*HNH), 87.7 ($CHNO_2$), the remaining signals could not be determined; m/z (EI) 420+422 (1:1, 14%, M^+), 317+319 (1:1, 100%, M^+-($C(CH_3)_3$+NO_2)), 192 (49%, PMPNHC$H^+C(CH_3)_3$); HRMS $C_{20}H_{25}(^{79}Br)N_2O_3$ calcd. 420.1043, found 420.1045.

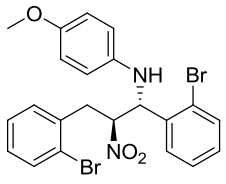
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(*o*-tolyl)propyl)-4-methoxyaniline (230h)



230h

Prepared using general procedure G. Nitroalkene **226a** (64 mg, 0.28 mmol) and 2-methylphenyl-imine (70 mg, 0.31 mmol) afforded crude *β*-nitroamine **230h** as a yellow oily solid (148 mg, 99% conv., *anti*:*syn* = 11:1); IR υ_{max} (neat) 3399 (N-H), 3057-2833 (C-H), 1549 (N-O), 1509 (C=C), 1233 (C-O, N-O), 1026 (C-O) cm^{-1}; ^1H NMR^{anti} (600 MHz, $CDCl_3$) δ 2.54 (3H, s, ArCH_3), 3.53 (1H, dd, *J* = 14.7, 11.2, CH_2), 3.59 (1H, dd, *J* = 14.7, 2.6, CH_2), 3.74 (3H, s, OCH_3), 4.19 (1H, br s, N*H*), 5.22 (1H, ddd, *J* = 11.1, 5.7, 2.6, C*H*NO_2), 5.29 (1H, d, *J* = 5.7, C*H*NH), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.78 (2H, dm, *J* = 8.9, Ar*H*), 7.12 (1H, m, Ar*H*), 7.22-7.27 (5H, m, Ar*H*), 7.52 (2H, m, Ar*H*); ^1H NMR^{syn} (600 MHz, $CDCl_3$) δ 2.62 (3H, s, ArCH_3), 3.32 (1H, dd, *J* = 14.1, 4.4, CH_2), 3.72 (3H, s, OCH_3), 5.09 (1H, d, *J* = 6.7, C*H*NH), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 19.4 (ArC*C*H_3), 34.9 (*C*H_2), 55.8 (O*C*H_3), 58.7 (*C*HNH), 90.4 (*C*HNO_2), 115.0 (Ar*C*H), 115.8 (Ar*C*H), 124.2 (Ar*C*CH_2), 126.3 (Ar*C*H), 127.0 (Ar*C*H), 128.1 (Ar*C*H), 128.5 (Ar*C*H), 129.5 (Ar*C*H), 131.5 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.3 (Ar*C*Br), 135.9 (Ar*C*CHNH), 136.0 (Ar*C*CH_3), 140.4 (Ar*C*N), 153.2 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 19.6 (ArC*C*H_3), 37.8 (*C*H_2), 55.7 (O*C*H_3), 57.3 (*C*HNPMP), 91.9 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 456+454 (1:1, 13%, M^+), 226 (100%, ArCH^+NHPMP); HRMS $C_{23}H_{23}(^{79}Br)N_2O_3$ calcd. 454.0887, found 454.0876.

_N_-((1_R_*,2_S_*)-1,3-Bis(2-bromophenyl)-2-nitropropyl)-4-methoxyaniline (230i)

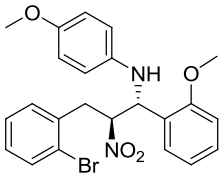


230i

Prepared using general procedure G. Nitroalkene **226a** (61 g, 0.27 mmol) and 2-bromophenyl-imine **224g** (85 mg, 0.29 mmol) afforded crude *β*-nitroamine **230i** as a yellow solid (196 mg, 99% conv., *anti*:*syn* = 10:1). The *anti* diastereomer could be obtained in pure form by recrystallisation from Et_2O/Pet. ether to give a yellow solid; mp 117-119 °C; R_f^{anti} 0.25 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3400 (N-H), 3063-2834 (C-H), 1550 (N-O), 1511 (C=C), 1244 (C-O and N-O), 1025 (C-O) cm^{-1}; ^1H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.40 (1H, br m, CH_2), 3.48 (1H, dd, *J* = 14.6, 11.7, CH_2), 3.71 (3H, s, OCH_3), 4.52 (1H, br s, N*H*), 5.40 (1H, br s, C*H*NH), 5.43 (1H, br d, *J* = 11.4, C*H*NO_2), 6.54 (2H, d, *J* = 8.9, Ar*H*), 6.73 (2H, dm, *J* = 8.9, Ar*H*), 7.11 (1H, m, Ar*H*), 7.19-7.23 (3H, m, Ar*H*), 7.33 (1H,

m, Ar*H*), 7.49 (1H, d, *J* = 7.9, Ar*H*), 7.52 (1H, br d, *J* = 7.4, Ar*H*), 7.64 (1H, dd, *J* = 8.0, 0.8, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 3.46 (1H, dd, *J* = 13.7, 4.7, CH_2), 3.63 (1H, dd, *J* = 14.0, 9.1, CH_2), 3.71 (3H, s, OCH_3), 4.95 (1H, d, *J* = 9.9, N*H*), 5.23 (1H, dd, *J* = 9.8, 5.6, C*H*NH), 5.35 (1H, dt, *J* = 9.7, 5.6, C*H*NO_2), 6.52 (2H, dm, *J* = 8.9, Ar*H*), 6.73 (2H, dm, *J* = 8.9, Ar*H*), 7.14-7.30 (6H, m, Ar*H*), 7.57 (1H, dd, *J* = 2.7, 0.9, Ar*H*), 7.58 (1H, dd, *J* = 2.6, 1.1, Ar*H*); ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 34.1 (*C*H_2), 55.7 (O*C*H_3), 61.2 (*C*HNHPMP), 88.8 (*C*HNO_2), 114.9 (Ar*C*H), 115.8 (Ar*C*H), 123.7 (Ar*C*CHNH), 124.3 (Ar*C*CH_2), 128.0 (Ar*C*H), 128.2 (Ar*C*H), 129.5 (Ar*C*H), 129.7 (Ar*C*H), 130.3 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 133.9 (Ar*C*H), 135.0 (Ar*C*Br), 136.0 (Ar*C*Br), 139.6 (Ar*C*N), 153.3 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 37.8 (*C*H_2), 55.7 (O*C*H_3), 58.3 (*C*HNH), 90.4 (*C*HNO_2), 114.9 (Ar*C*H), 115.0 (Ar*C*H), the remaining signals could not be determined; m/z (EI) 522+520+518 (10:20:10%, M^+), 292+ 290 (1:1, 100%, ArCH^+NHPMP); HRMS $C_{22}H_{20}(^{79}Br)_2N_2O_3$ calcd. 517.9835, found 517.9843; Anal. calcd. for $C_{22}H_{20}Br_2N_2O_3$: C, 50.79; H, 3.88; N, 5.38; found: C, 50.65; H, 3.85; N, 5.28%.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(2-methoxyphenyl)-2-nitropropyl)-4-methoxyaniline (230j)

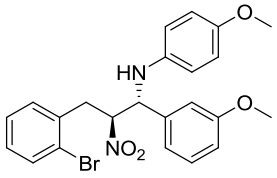


230j

Prepared using general procedure G. Nitroalkene **226a** (52 mg, 0.23 mmol) and 2-methoxyphenyl-imine (61 mg, 0.25 mmol) afforded crude *β*-nitroamine **230j** as a yellow oil (134 mg, 96% conv., *anti*:*syn* = 11.5:1); IR υ_{max} (neat) 3402 (N-H), 3063-2836 (C-H), 1549 (N-O), 1510 (C=C). 1488, 1464, 1439, 1235 (N-O, C-O), 1023 (C-O) cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.40 (1H, dd, *J* = 14.7, 11.5, CH_2), 3.70 (1H, m, CH_2), 3.74 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.61 (1H, br s, N*H*), 5.13 (1H, d, *J* = 5.6, C*H*NH), 5.54 (1H, ddd, *J* = 11.5, 7.4, 2.4, C*H*NO_2), 6.70 (2H, dm, *J* = 8.9, Ar*H*), 6.78 (2H, dm, *J* = 8.9, Ar*H*), 6.92 (1H, td, *J* = 7.5, 0.7, Ar*H*), 6.93 (1H, d, *J* = 8.2, Ar*H*), 7.12 (1H, m, Ar*H*), 7.19-7.30 (4H, m, Ar*H*), 7.55 (1H, dd, *J* = 8.0, 0.8, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 3.19 (1H, dd, *J* = 14.0, 3.8, CH_2), 3.36 (1H, dd, *J* = 14.2, 10.4, CH_2), 4.76 (1H, br s, N*H*), 5.06 (1H, d, *J* = 6.7, C*H*NH), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 36.4 (*C*H_2), 55.7 (O*C*H_3), 55.8 (O*C*H_3), 60.1 (*C*HNH), 90.0 (*C*HNO_2),

111.3 (Ar*C*H), 114.9 (Ar*C*H), 115.9 (Ar*C*H), 121.1 (Ar*C*H), 124.4 (Ar*C*CH_2), 125.0 (Ar*C*CHNH), 128.0 (Ar*C*H), 129.3 (Ar*C*H), 129.7 (Ar*C*H), 129.8 (Ar*C*H), 131.6 (Ar*C*H), 133.2 (Ar*C*H), 135.7 (Ar*C*Br), 140.7 (Ar*C*N), 153.0 (Ar*C*O), 157.3 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 38.4 (*C*H_2), 55.5 (O*C*H_3), 55.5 (O*C*H_3), 90.6 (*C*HNO_2), the remaining signals could not be determined; m/z (EI) 470+472 (1:1, 6%, M^+), 242 (100%, ArCH^+NHPMP); HRMS $C_{23}H_{23}(^{79}Br)N_2O_4$ calcd. 470.0836, found 470.0820.

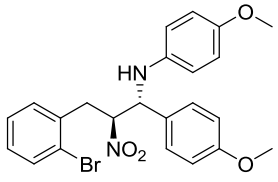
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(3-methoxyphenyl)-2-nitropropyl)-4-methoxyaniline (230k)



230k

Prepared using general procedure G. Nitroalkene **226a** (177 mg, 0.776 mmol) and 3-methoxyphenyl-imine (206 mg, 0.854 mmol) afforded crude *β*-nitroamine **230k** as a yellow oil (486 mg, 99% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3381 (N-H), 3057-2834 (C-H), 1551 (N-O), 1511 (C=C), 1242 (C-O), 1037 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.45 (1H, dd, *J* = 14.8, 11.2, C*H*$_2$), 3.56 (1H, dd, *J* = 14.8, 2.7, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.29 (1H, br s, N*H*), 4.93 (1H, d, *J* = 5.9, C*H*NH), 5.21 (1H, ddd, *J* = 11.1, 6.0, 2.7, C*H*NO_2), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.76 (2H, dm, *J* = 8.9, Ar*H*), 6.87 (1H, dd, *J* = 8.0, 2.3, Ar*H*), 6.96 (1H, t, *J* = 2.0, Ar*H*), 7.02 (1H, d, *J* = 7.7, Ar*H*), 7.12 (1H, td, *J* = 7.6, 1.8, Ar*H*), 7.18 (1H, dd, *J* = 7.7, 1.8, Ar*H*), 7.22 (1H, td, *J* = 7.4, 1.0, Ar*H*), 7.30 (1H, t, *J* = 7.9, Ar*H*), 7.53 (1H, dd, *J* = 8.0, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.8 (*C*H_2), 55.4 (O*C*H_3), 55.8 (O*C*H_3), 62.1 (*C*HNH), 91.7 (*C*HNO_2), 113.2 (Ar*C*H), 113.9 (Ar*C*H), 114.9 (Ar*C*H), 115.9 (Ar*C*H), 119.5 (Ar*C*H), 124.4 (Ar*C*CH_2), 128.1 (Ar*C*H), 129.5 (Ar*C*H), 130.3 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.1 (Ar*C*Br), 139.2 (Ar*C*CHNH), 140.1 (Ar*C*N), 153.2 (Ar*C*O), 160.1 (Ar*C*O); m/z (EI) 470+472 (1:1, 4%, M^+), 349+351 (1:1, 2%, M^+-PMPNH), 242 (53%, ArCH^+NHPMP); HRMS $C_{23}H_{23}(^{79}Br)N_2O_4$ calcd. 470.0836, found 470.0845.

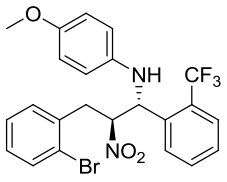
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(4-methoxyphenyl)-2-nitropropyl)-4-methoxyaniline (230l)



230l

Prepared using general procedure G. Nitroalkene **226a** (1.09 g, 4.79 mmol) and 4-methoxyphenyl-imine **224h** (1.27 g, 5.27 mmol) afforded crude *β*-nitroamine **230l** as a yellow oily solid (2.70 g, 99% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3401 (N-H), 3065-2835 (C-H), 1551 (N-O), 1510 (C=C), 1244 (C-O, N-O), 1032 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.44 (1H, dd, *J* = 14.8, 11.1, C*H*$_2$), 3.57 (1H, dd, *J* = 14.7, 2.6, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 4.28 (1H, br s, N*H*), 4.90 (1H, d, *J* = 5.7, C*H*NH), 5.19 (1H, ddd, *J* = 11.0, 6.1, 2.7, C*H*NO_2), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.76 (2H, dm, *J* = 8.9, Ar*H*), 6.90 (2H, dm, *J* = 8.7, Ar*H*), 7.13 (1H, td, *J* = 7.6, 1.7, Ar*H*), 7.18 (1H, dd, *J* = 7.6, 1.6, Ar*H*), 7.22 (1H, td, *J* = 7.5, 0.7, Ar*H*), 7.33 (2H, dm, *J* = 8.6, Ar*H*), 7.54 (1H, dd, *J* = 7.9, 0.6, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.0 (*C*H_2), 55.4 (O*C*H_3), 55.8 (O*C*H_3), 61.6 (*C*HNH), 91.9 (*C*HNO_2), 114.5 (Ar*C*H), 114.9 (Ar*C*H), 115.9 (Ar*C*H), 124.4 (Ar*C*CH_2), 128.1 (Ar*C*H), 128.4 (Ar*C*H), 129.4 (Ar*C*CHNH), 129.5 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 135.2 (Ar*C*Br), 140.1 (Ar*C*N), 153.1 (Ar*C*O), 159.8 (Ar*C*O); m/z (CI) 472+470 (1:1, 7%, M^+), 426+424 (1:1, 20%, M^+-NO_2), 242 (100%, PMPCH^+NHPMP); HRMS $C_{23}H_{23}(^{79}Br)N_2O_4$ calcd. 470.0836, found 470.0850.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(2-(trifluoromethyl)phenyl)propyl)-4-methoxyaniline (230m)

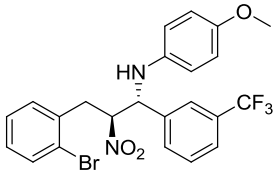


230m

Prepared using general procedure G. Nitroalkene **226a** (739 mg, 3.24 mmol) and 2-trifluoromethylphenyl-imine (996 mg, 3.57 mmol) afforded crude *β*-nitroamine **230m** as a yellow oil (2.00 g, >99% conv., *anti*:*syn* = 7.5:1); IR υ_{max} (neat) 3392 (N-H), 3068-2835 (C-H), 1552 (N-O), 1511 (C=C), 1309, 1243 (C-O, N-O), 1160 (C-F), 1115 (C-F), 1034 (C-O) cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.45 (1H, dd, *J* = 14.6, 2.1, C*H*$_2$), 3.55 (1H,

dd, *J* = 14.6, 11.7, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 4.39 (1H, br s, N*H*), 5.32 (1H, ddd, *J* = 11.7, 4.5, 2.3, C*H*NH), 5.53 (1H, d, *J* = 4.3, C*H*NO$_2$), 6.61 (2H, dm, *J* = 8.9, Ar*H*), 6.75 (2H, dm, *J* = 8.9, Ar*H*), 7.09-7.13 (1H, m, Ar*H*), 7.22 (2H, d, *J* = 4.2, Ar*H*), 7.47-7.50 (2H, m, Ar*H*), 7.61 (1H, t, *J* = 7.5. Ar*H*), 7.79 (1H, d, *J* = 7.7, Ar*H*), 7.90 (1H, d, *J* = 7.9, Ar*H*); ^{1}H NMR^{syn} (600 MHz, CDCl$_3$) δ 3.43-3.48 (2H, m, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.92 (1H, br s, N*H*), 5.23 (1H, br s, C*H*NH), 5.28-2.31 (1H, m, C*H*NO$_2$), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, CDCl$_3$) δ 33.7 (*C*H$_2$), 55.7 (*C*HNH), 57.9 (O*C*H$_3$), 90.2 (*C*HNO$_2$), 114.9 (Ar*C*H), 116.0 (Ar*C*H), 124.2 (Ar*C*CH$_2$), 124.4 (1C, q, *J* = 274.2, ArC*C*F$_3$), 127.2 (1C, q, *J* = 6.0, Ar*C*H), 128.1 (Ar*C*H), 129.0 (2 x Ar*C*H), 129.5 (Ar*C*H), 131.7 (Ar*C*H), 132.8 (Ar*C*H), 133.3 (Ar*C*H), 134.8 (Ar*C*Br), 136.6 (Ar*C*CHNH), 139.5 (Ar*C*N), 153.4 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, CDCl$_3$) δ 34.0 (*C*H$_2$), 55.6 (*C*HNH), 55.7 (O*C*H$_3$), 89.7 (*C*HNO$_2$), the remaining signals could not be determined; ^{19}F NMR^{anti} (282 MHz, CDCl$_3$) δ -58.3 (3F, s, C*F*$_3$); m/z (EI) 508+510 (1:1, 16%, M$^+$), 279 (100%, ArCH$^+$NHPMP); HRMS C$_{23}$H$_{20}$(^{79}Br)F$_3$N$_2$O$_3$ calcd. 508.0604, found 508.0615.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(3-(trifluoromethyl)phenyl)propyl)-4-methoxyaniline (230n)

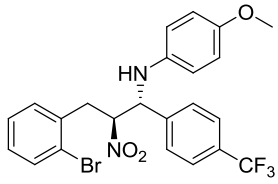


230n

Prepared using general procedure G. Nitroalkene **226a** (142 mg, 0.623 mmol) and 3-trifluoromethylphenyl-imine (191 mg, 0.685 mmol) afforded crude *β*-nitroamine **230n** as a yellow oil (448 mg, >99% conv., *anti*:*syn* = >20:1); IR υ$_{max}$ (neat) 3405 (N-H), 3061-2836 (C-H), 1552 (N-O), 1511 (C=C), 1327 (N-O), 1243 (C-O), 1165 (C-F), 1123 (C-F), 1072, 1034, 1026 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.45 (1H, dd, *J* = 14.8, 10.5, C*H*$_2$), 3.49 (1H, dd, *J* = 14.8, 3.3, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.34 (1H, br s, N*H*), 5.03 (1H, d, *J* = 5.7, C*H*NH), 5.21 (1H, ddd, *J* = 10.5, 5.6, 3.4, C*H*NO$_2$), 6.59 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 9.0, Ar*H*), 7.14 (1H, td, *J* = 7.6, 1.7, Ar*H*), 7.18 (1H, dd, *J* = 7.7, 1.8, Ar*H*), 7.23 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.52 (1H, t, *J* = 7.7, Ar*H*), 7.53 (1H, dd, *J* = 8.0, 1.1, Ar*H*), 7.63 (1H, t, *J* = 9.4, Ar*H*), 7.72 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, CDCl$_3$) δ 35.5 (*C*H$_2$), 55.7 (O*C*H$_3$), 61.8 (*C*HNH), 91.4 (*C*HNO$_2$), 115.0 (Ar*C*H), 116.0 (Ar*C*H), 124.1 (1C, q, *J* = 272.5, *C*F$_3$), 124.2 (1C, q, *J* = 3.5, Ar*C*H), 124.3 (Ar*C*CH$_2$), 125.7 (1C, q, *J* = 3.5,

Ar*C*H), 128.1 (Ar*C*H), 129.7 (Ar*C*H), 129.8 (Ar*C*H), 130.7 (Ar*C*H), 131.5 (1C, q, *J* = 32.4, Ar*C*CF_3), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 134.6 (Ar*C*Br), 138.8 (Ar*C*CHN), 139.5 (Ar*C*N), 153.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.0; m/z (EI) 508+510 (5%, M^+), 338+340 (5%, M^+-(NHPMP+NO_2)), 279 (100%, ArCH^+NHPMP); HRMS $C_{23}H_{20}(^{79}Br)F_3N_2O_3$ calcd. 508.0604, found 508.0619.

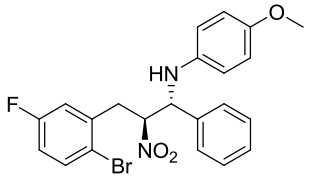
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(4-(trifluoromethyl)phenyl)propyl)-4-methoxyaniline (230o)



230o

Prepared using general procedure G. Nitroalkene **226a** (211 mg, 0.925 mmol) and 4-trifluoromethylphenyl-imine **224i** (284 mg, 1.02 mmol) afforded crude *β*-nitroamine **230o** as a yellow oil (550 mg, 99% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3395 (N-H), 3057-2835 (C-H), 1552 (N-O), 1510 (C=C), 1323, 1241 (N-O, C-O), 1165 (C-F), 1121 (C-F), 1113 (C-F), 1066, 1035, 1027 (C-O), 1017 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.46 (1H, dd, *J* = 14.8, 11.0, C*H*$_2$), 3.55 (1H, dd, *J* = 14.7, 2.7, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.33 (1H, br s, N*H*), 5.02 (1H, s, C*H*NH), 5.22 (1H, ddd, *J* = 10.9, 6.0, 2.8, C*H*NO_2), 6.59 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 8.9, Ar*H*), 7.14 (1H, td, *J* = 7.6, 1.7, Ar*H*), 7.18 (1H, dd, *J* = 7.7, 1.7, Ar*H*), 7.23 (1H, td, *J* = 7.4, 1.0, Ar*H*), 7.55 (1H, dd, *J* = 8.1, 1.0, Ar*H*), 7.56 (2H, d, *J* = 8.3, Ar*H*), 7.65 (2H, d, *J* = 8.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.8 (*C*H_2), 55.7 (O*C*H_3), 61.7 (*C*HNH), 91.4 (*C*HNO_2), 115.0 (Ar*C*H), 116.0 (Ar*C*H), 124.0 (1C, q, *J* = 272.2, *C*F_3), 124.3 (Ar*C*CH_2), 126.2 (1C, q, *J* = 3.5, Ar*C*H), 127.8 (Ar*C*H), 128.2 (Ar*C*H), 129.7 (Ar*C*H), 131.0 (1C, q, *J* = 32.5, Ar*C*CF_3), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 134.6 (Ar*C*Br), 139.4 (Ar*C*N), 141.7 (Ar*C*CHNH), 153.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.0 (3F, s, C*F*$_3$); m/z (EI) 508+510 (1:1, 15%, M^+), 280 (ArCH^+NHPMP); HRMS $C_{23}H_{20}(^{79}Br)F_3N_2O_3$ calcd. 508.0604, found 508.0616.

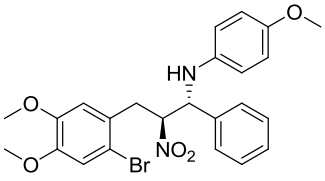
_N_-((1_R_*,2_S_*)-3-(2-Bromo-5-fluorophenyl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230p)



230p

Prepared using general procedure G. Nitroalkene **226b** (118 mg, 0.480 mmol) and imine **224a** (111 mg, 0.528 mmol) afforded crude *β*-nitroamine **230p** as a yellow oil (304 mg, >99% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3401 (N-H), 3066-2834 (C-H), 1551 (N-O), 1510 (C=C), 1470 (N-O), 1235 (C-O), 1030 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (1H, dd, *J* = 14.8, 11.0, C*H*$_2$), 3.51 (1H, dd, *J* = 14.8, 2.7, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.27 (1H, br s, N*H*), 4.97 (1H, d, *J* = 5.6, C*H*NH), 5.20 (1H, ddd, *J* = 11.0, 5.9, 2.7, C*H*NO_2), 6.63 (2H, dm, *J* = 8.9, Ar*H*), 6.76 (2H, dm, *J* = 8.9, Ar*H*), 6.87 (1H, td, *J* = 8.3, 3.0, Ar*H*), 6.94 (1H, dd, *J* = 8.9, 3.0, Ar*H*), 7.35 (1H, m, Ar*H*), 7.38-7.43 (4H, m, Ar*H*), 7.48 (1H, dd, *J* = 8.8, 5.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.7 (*C*H_2), 55.8 (O*C*H_3), 62.2 (*C*HNH), 91.4 (*C*HNO_2), 114.9 (Ar*C*H), 116.0 (Ar*C*H), 116.7 (1C, d, *J* = 22.6, Ar*C*H), 118.5 (1C, d, *J* = 3.1, Ar*C*CH_2), 118.8 (1C, d, *J* = 23.2, Ar*C*H), 127.2 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 134.4 (1C, d, *J* = 7.9, Ar*C*H), 137.1 (1C, d, *J* = 7.7, Ar*C*Br), 137.3 (Ar*C*CHNH), 139.9 (Ar*C*N), 153.3 (Ar*C*O), 161.9 (1C, d, *J* = 248.5, Ar*C*F); ^{19}F NMR (126 MHz, $CDCl_3$) δ -114.1 (1F, m, ArC*F*); m/z (EI) 458+460 (5%, M^+), 290+292 (10%, M^+-(NHPMP+NO_2), 212 (100%, PhCH^+NHPMP); HRMS $C_{22}H_{20}(^{79}Br)FN_2O_3$ calcd. 458.0636, found 458.0635.

_N_-((1_R_*,2_S_*)-3-(2-Bromo-4,5-dimethoxyphenyl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230q)

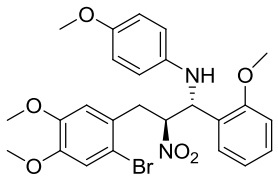


230q

Prepared using general procedure G. Nitroalkene **226c** (136 mg, 0.472 mmol) and imine **224a** (110 mg, 0.519 mmol) afforded crude *β*-nitroamine **230q** as a yellow solid (273 mg, >95% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3389 (N-H), 3005-2837 (C-H), 1551 (N-O),

1509 (C=C), 1260, 1243 (C-O), 1219, 1166 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.35 (1H, dd, *J* = 14.9, 11.1, CH_2), 3.44 (1H, dd, *J* = 14.8, 2.7, CH_2), 3.72 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.28 (1H, br d, *J* = 4.6, N*H*), 4.92 (1H, br d, *J* = 4.9, C*H*Ph), 5.16 (1H, ddd, *J* = 11.0, 5.7, 2.7, C*H*NO_2), 6.59 (2H, dm, *J* = 8.9, Ar*H*), 6.64 (1H, s, Ar*H*), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 6.97 (1H, s, Ar*H*), 7.33 (1H, m, Ar*H*), 7.36-7.41 (4H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.0 (*C*H_2), 55.3 (O*C*H_3), 55.7 (O*C*H_3), 55.8 (O*C*H_3), 61.7 (*C*HPh), 91.6 (*C*HNO_2), 113.6 (Ar*C*H), 113.8 (Ar*C*CH_2), 114.5 (Ar*C*H), 115.4 (Ar*C*H), 115.5 (Ar*C*H), 126.5 (Ar*C*Br), 126.8 (Ar*C*H), 128.3 (Ar*C*H), 128.7 (Ar*C*H), 137.1 (Ar*C*CHN), 139.6 (Ar*C*N), 148.2 (Ar*C*O), 148.7 (Ar*C*O), 152.7 (Ar*C*O); m/z (EI) 500+502 (1:1, 2%, M^+), 289+291 (1:1, 16%, M^+-PMPNHBn), 242+244 (1:1, 46%, M^+-(PMPNHCHPh+NO_2)), 211 (91%, $PhCH^+NHPMP$); HRMS $C_{24}H_{25}(^{79}Br)N_2O_5$ calcd. 500.0941, found 500.0936.

_N_-((1_R_*,2_S_*)-3-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-methoxyphenyl)-2-nitropropyl)-4-methoxyaniline (230r)

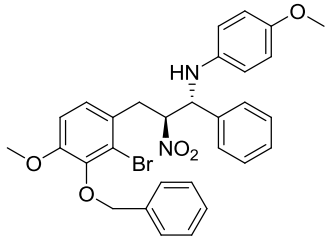


230r

Prepared using general procedure G. Nitroalkene **226c** (775 mg, 2.69 mmol) and 2-methoxyphenyl-imine (714 mg, 2.96 mmol) afforded crude *β*-nitroamine **230r** as a yellow oil (2.27 g, >99% conv., *anti*:*syn* = 5:1); IR υ_{max} (neat) 3392 (N-H), 3001-2838 (C-H), 1550 (N-O), 1509 (C=C), 1258 (N-O), 1237 (C-O), 1219 (C-O), 1164, 1025 (C-O) cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.29 (1H, dd, *J* = 14.8, 11.4, CH_2), 3.57 (1H, dd, *J* = 14.8, 1.9, CH_2), 3.72 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.56 (1H, br s, N*H*), 5.09 (1H, br d, *J* = 6.1, C*H*NHAr), 5.45 (1H, ddd, *J* = 11.4, 7.1, 2.5, C*H*NO_2), 6.65 (2H, dm, *J* = 8.9, Ar*H*), 6.65 (1H, s, Ar*H*), 6.75 (2H, dm, *J* = 8.9, Ar*H*), 6.90-6.93 (2H, m, Ar*H*), 6.97 (1H, s, Ar*H*), 7.22 (1H, dd, *J* = 7.5, 1.5, Ar*H*), 7.26-7.29 (1H, m, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 3.21 (1H, dd, *J* = 14.0, 5.9, CH_2), 4.82 (1H, br s, N*H*), 4.92 (1H, br s, C*H*NHAr), 5.45 (1H, dt, *J* = 9.1, 6.5, C*H*NO_2), 6.54 (2H, dm, *J* = 8.9, Ar*H*), 6.62 (1H, s, Ar*H*), 6.69 (2H, dm, *J* = 8.9, Ar*H*), 7.00 (1H, s, Ar*H*), 7.18 (1H, dd, *J* = 7.7, 1.5, Ar*H*), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 36.0 (*C*H_2), 55.7 (O*C*H_3), 55.8 (O*C*H_3), 56.1 (O*C*H_3), 56.2 (O*C*H_3),

59.9 (*C*HNHAr), 90.3 (*C*HNO$_2$), 111.2 (ArCH), 114.0 (ArCH), 114.2 (Ar*C*CH$_2$), 114.9 (Ar*C*H), 115.7 (Ar*C*H), 115.8 (Ar*C*H), 121.1 (Ar*C*H), 125.0 (Ar*C*CHN), 127.5 (Ar*C*Br), 129.6 (Ar*C*H), 129.8 (Ar*C*H), 140.6 (Ar*C*N), 148.5 (Ar*C*O), 149.0 (Ar*C*O), 153.0 (Ar*C*O), 157.3 (Ar*C*O); ^{13}C NMR^{syn} (151 MHz, CDCl$_3$) δ 37.9 (*C*H$_2$), 55.5 (O*C*H$_3$), 55.6 (O*C*H$_3$), 55.7 (O*C*H$_3$), 55.8 (O*C*H$_3$), 57.2 (*C*HNHAr), 90.0 (*C*HNO$_2$); the remaining signals could not be determined; m/z (EI) 530+532 (1:1, 4%, M$^+$), 242 (100%, ArCH$^+$NHPMP); HRMS $C_{25}H_{27}(^{79}Br)N_2O_6$ calcd. 530.1047, found 530.1055.

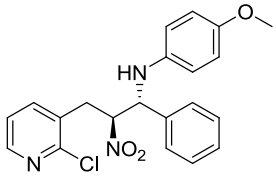
_N_-((1_R_*,2_S_*)-3-(3-(Benzyloxy)-2-bromo-4-methoxyphenyl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230s)



230s

Prepared using general procedure G. Nitroalkene **226d** (426 mg, 1.17 mmol) and imine **224a** (272 mg, 1.29 mmol) afforded crude *β*-nitroamine **230s** as a yellow oily foam (835 mg, >99% conv., *anti*:*syn* = >20:1); IR υ_{max} (neat) 3389 (N-H), 3065-2836 (C-H), 1551 (N-O), 1511 (C=C), 1485, 1268, 1241 (C-O), 1032 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.41 (1H, dd, *J* = 14.9, 11.1, C*H*$_2$), 3.54 (1H, dd, *J* = 14.9, 2.6, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 4.32 (1H, s, N*H*), 4.95 (1H, d, *J* = 5.9, C*H*Ph), 5.03 (2H, s, C*H*$_2$Ph), 5.19 (1H, ddd, *J* = 11.1, 5.9, 2.7, C*H*NO$_2$), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.76 (2H, dm, *J* = 8.9, Ar*H*), 6.79 (1H, d, *J* = 8.6, Ar*H*), 6.93 (1H, d, *J* = 8.5, Ar*H*), 7.33-7.44 (8H, m, Ar*H*), 7.55-7.56 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, CDCl$_3$) δ 35.5 (*C*H$_2$), 55.8 (O*C*H$_3$), 56.2 (O*C*H$_3$), 62.1 (*C*HNH), 74.7 (O*C*H$_2$), 92.1 (*C*HNO$_2$), 111.5 (Ar*C*H), 114.9 (Ar*C*H), 115.9 (Ar*C*H), 120.4 (Ar*C*CH$_2$), 126.6 (Ar*C*H), 127.3 (Ar*C*H), 127.7 (Ar*C*Br), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 129.2 (Ar*C*H), 137.2 (Ar*C*CH$_2$O), 137.6 (Ar*C*HNH), 140.1 (Ar*C*N), 145.6 (Ar*C*OCH$_2$), 153.1 (Ar*C*O), 153.3 (Ar*C*O); m/z (EI) 576+578 (1:1, 2%, M$^+$), 365+367 (1:1, 11%, M$^+$-PhCHNHPMP), 319+321 (1:1, 54%, M$^+$-(PhCHNHPMP+NO$_2$)), 212 (100%, PhCH$^+$NHPMP); HRMS $C_{30}H_{29}(^{79}Br)N_2O_5$ calcd. 576.1254, found 576.1239.

***N*-((1*R**,2*S**)-3-(2-Chloropyridin-3-yl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230t)**



230t

Prepared using general procedure G. Nitroalkene **226e** (41 mg, 0.22 mmol) and imine **224a** (52 mg, 0.24 mmol) afforded crude *β*-nitroamine **230t** as a yellow oil (98 mg, >95% conv., *anti*:*syn* >95:5); IR υ_{max} (neat) 3372 (N-H), 3059-2834 (C-H), 1550 (N-O), 1510 (C=C), 1410 (C=N), 1238 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.41 (1H, dd, *J* = 14.9, 11.2, C*H*$_2$), 3.52 (1H, dd, *J* = 14.9, 2.4, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 4.21 (1H, br s, N*H*), 4.99 (1H, d, *J* = 5.8, C*H*Ph), 5.21 (1H, ddd, *J* = 11.2, 5.9, 2.5, C*H*NO_2), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.75 (2H, dm, *J* = 8.9, Ar*H*), 7.16 (1H, dd, *J* = 7.6, 4.8, Ar*H*), 7.33-7.40 (5H, m, Ar*H*), 7.53 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 8.30 (1H, dd, *J* = 4.7, 1.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 33.0 (*C*H_2), 55.8 (O*C*H_3), 62.2 (*C*HPh), 90.9 (*C*HNO_2), 114.9 (Ar*C*H), 116.1 (Ar*C*H), 123.1 (Ar*C*H), 127.0 (Ar*C*H), 128.9 (Ar*C*H), 129.3 (Ar*C*H), 130.3 (Ar*C*CH_2), 137.1 (Ar*C*CHN), 139.7 (Ar*C*N), 140.4 (Ar*C*H), 149.1 (Ar*C*H), 151.2 (Ar*C*Cl), 153.3 (Ar*C*O); m/z (EI) 397 (3%, M^+), 212 (31%, M^+-$C_7H_6ClN_2O_2$); HRMS $C_{21}H_{20}ClN_3O_3$ calcd. 397.1188, found 397.1196.

4.4.5 Preparation of *β*-Nitroacetamides

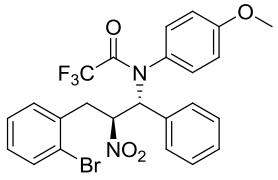
General Procedure H

To a solution of crude *β*-nitroamine (1.00 mmol) in CH_2Cl_2 (10.0 mL) at -78 °C was added DIPEA (2.50 mmol) quickly followed by the dropwise addition of TFAA (2.50 mmol). The mixture was stirred at -78 °C for 60 min before being allowed to warm to room temperature over 30 min. The reaction was quenched by the addition of 2 M HCl (15 mL). The phases were separated and the aqueous further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude *β*-nitroacetamide which was purified by flash column chromatography.

General Procedure I

To a solution of crude *β*-nitroamine (1.00 mmol) in CH_2Cl_2 (10.0 mL) at -78 °C was added pyridine (5.00 mmol) quickly followed by the dropwise addition of TFAA (5.00 mmol). The mixture was stirred at -78 °C for 60 min before being allowed to warm to room temperature over 30 min. The reaction was quenched by the addition of 2 M HCl (15 mL). The phases were separated and the aqueous further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude *β*-nitroacetamide which was purified by flash column chromatography.

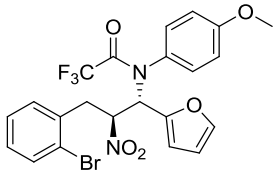
***N*-[(1*R**,2*S**)-3-(2-Bromophenyl)-2-nitro-1-phenylpropyl]-*N*-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232a)**



232a

Prepared using general procedure H. Crude *β*-nitroamine **230a** (1.31 mmol) afforded crude *β*-nitroacetamide **232a** as a brown oil. Purification by flash column chromatography (40% CH_2Cl_2/Pet. ether followed by 10% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232a** as a white solid (500 mg, 71%, *anti*:*syn* >20:1); mp 118-120 °C; R_f 0.24 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3062-2841 (C-H), 1699 (C=O), 1559 (N-O), 1512 (C=C), 1255, 1183 (C-F), 1169 (C-F), 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.61 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$), 3.79 (1H, dd, *J* = 14.5, 3.8, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.76 (1H, td, *J* = 11.2, 3.6, C*H*NO_2), 6.27 (1H, d, *J* = 9.0, Ar*H*), 6.31 (1H, d, *J* = 11.3, C*H*Ph), 6.63 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.92 (1H, dd, *J* = 8.7, 2.9, Ar*H*), 7.08 (2H, d, *J* = 7.3, Ar*H*), 7.16-7.33 (6H, m, Ar*H*), 7.41 (1H, dd, *J* = 8.7, 1.4, Ar*H*), 7.61-7.63 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.7 (*C*H_2), 55.6 (O*C*H_3), 64.8 (*C*HPh), 87.2 (*C*HNO_2), 113.8 (Ar*C*H), 114.3 (Ar*C*H), 116.3 (1C, q, *J* = 288.7, *C*F_3), 124.1 (Ar*C*CH_2), 127.6 (Ar*C*CHN), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 129.6 (Ar*C*H), 129.8 (Ar*C*H), 129.9 (Ar*C*H), 130.8 (Ar*C*H), 131.7 (Ar*C*H), 132.4 (Ar*C*H), 132.8 (Ar*C*Br), 133.3 (Ar*C*H), 133.9 (Ar*C*N), 158.3 (1C, q, *J* = 35.7, *C*CF_3), 160.4 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.1 (3F, s, C*F*$_3$); m/z (ESI^+) 559+561 (1:1, 100%, M^++Na); HRMS $C_{24}H_{20}(^{79}Br)F_3N_2O_4Na$ calcd. 559.0430, found 559.0451; Anal. calcd. for $C_{24}H_{20}BrF_3N_2O_4$: C, 53.65; H, 3.75; N, 5.21; found: C, 53.93; H, 3.84; N, 4.95%.

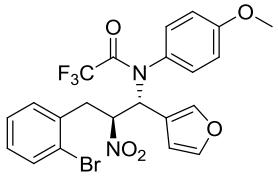
_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-1-(furan-2-yl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232b)



232b

Prepared using general procedure H. Crude *β*-nitroamine **230b** (4.42 mmol) afforded crude *β*-nitroacetamide **232b** as a brown solid. Purification by flash column chromatography (45% CH_2Cl_2/Pet. ether) yielded pure *β*-nitroacetamide **232b** as a white solid (2.03 g, 87%, *anti*:*syn* = 13.5:1). Subsequent recrystallisation from toluene/Pet. ether gave *β*-nitroacetamide **232b** as a single *anti* diastereomer (1.63 g, 70%); mp 134-137 °C; R_f 0.44 (45% CH_2Cl_2/Pet. ether); IR υ_{max} (neat) 3130-2841 (C-H), 1701 (C=O), 1556 (N-O), 1510 (C=C), 1253 (N-O), 1206 (C-O), 1180 (C-F), 1154 (C-F), 1029 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.51 (1H, dd, *J* = 14.3, 11.7, C*H*$_2$), 3.71 (1H, dd, *J* = 14.3, 3.8, C*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.57 (1H, td, *J* = 11.1, 3.7, C*H*NO_2), 6.26 (1H, dd, *J* = 3.2, 1.4, Furyl-4-*H*), 6.27 (1H, d, *J* = 3.4, Furyl-3-*H*), 6.45 (1H, d, *J* = 10.7, C*H*NTFA), 6.49 (1H, d, *J* = 8.1, Ar*H*), 6.71 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.93 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 7.14 (1H, dd, *J* = 7.7, 1.4, Ar*H*), 7.19 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.27 (1H, td, *J* = 7.5, 0.9, Ar*H*), 7.32 (1H, d, *J* = 1.1, Furyl-5-*H*), 7.48 (1H, dd, *J* = 8.7, 2.1, Ar*H*), 7.61 (1H, dd, *J* = 7.9, 0.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.3 (*C*H_2), 55.6 (O*C*H_3), 58.4 (*C*HNTFA), 86.3 (*C*HNO_2), 111.0 (Furyl-4-*C*H), 112.1 (Furyl-3-*C*H), 113.9 (Ar*C*H), 114.5 (Ar*C*H), 116.2 (1C, q, *J* = 288.6, *C*F_3), 124.1 (Ar*C*CH_2), 128.0 (Ar*C*N), 128.4 (Ar*C*H), 130.0 (Ar*C*H), 130.6 (Ar*C*H), 131.0 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 133.6 (Ar*C*Br), 143.4 (Furyl-5-*C*H), 145.9 (Furyl-2-*C*), 158.2 (1C, q, *J* = 36.0, *C*CF_3), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$); m/z (CI) 527+529 (1:1, 4%, M^+), 480+482 (1:1, 100%, M^+-NO_2); HRMS $C_{22}H_{18}(^{79}Br)F_3N_2O_5$ calcd. 527.0429, found 527.0438; Anal. calcd. for $C_{22}H_{18}BrF_3N_2O_5$: C, 50.11; H, 3.44; N, 5.31; found: C, 50.23; H, 3.50; N, 5.20%.

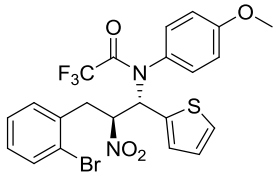
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(furan-3-yl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232c)



232c

Prepared using general procedure H. Crude *β*-nitroamine **230c** (5.65 mmol) afforded crude *β*-nitroacetamide **232c** as a brown oily solid. Purification by flash column chromatography (50% CH_2Cl_2/Pet. ether followed by 20% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232c** as a white solid (2.47 g, 83%, *anti*:*syn* = 14:1). Subsequent recrystallisation from toluene/Pet. ether gave *β*-nitroacetamide **232c** as a single *anti* diastereomer (2.06 g, 69%); mp 120-122 °C; R_f 0.36 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3137-2842 (C-H), 1697 (C=O), 1557 (N-O), 1510 (C=C), 1253 (N-O), 1207 (C-O), 1180 (C-F), 1155 (C-F), 1025 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.49 (1H, dd, *J* = 14.3, 11.6, C*H*$_2$), 3.71 (1H, dd, *J* = 14.3, 3.5, C*H*$_2$), 3.85 (3H, s, OC*H*$_3$), 5.67 (1H, m, C*H*NO_2), 5.91 (1H, br m, C*H*NTFA), 6.11 (1H, s, Furyl-4-*H*), 6.80 (1H, br d, *J* = 8.8, Ar*H*), 6.82 (1H, dd, *J* = 8.7, 2.6, Ar*H*), 6.93 (1H, dd, *J* = 8.8, 2.7, Ar*H*), 7.14 (1H, dd, *J* = 7.6, 1.6, Ar*H*), 7.18 (1H, td, *J* = 7.7, 1.7, Ar*H*), 7.26 (1H, td, *J* = 7.5, 1.2, Ar*H*), 7.30 (1H, app t, *J* = 1.1, Furyl-5-*H*), 7.33 (1H, s, Furyl-2-*H*), 7.35 (1H, br d, *J* = 9.1, Ar*H*), 7.60 (1H, dd, *J* = 8.0, 1.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.3 (*C*H_2), 55.7 (O*C*H_3), 58.8 (*C*HNPMP), 88.3 (*C*HNO_2), 110.5 (Furyl-4-*C*H), 114.2 (Ar*C*H), 114.7 (Ar*C*H), 116.2 (1C, q, *J* = 288.6, *C*F_3), 117.8 (Furyl-3-*C*), 124.2 (Ar*C*CH_2), 128.3 (Ar*C*H), 128.8 (Ar*C*N), 129.8 (Ar*C*H), 130.4 (Ar*C*H), 131.5 (Ar*C*H), 131.8 (Ar*C*H), 133.3 (Ar*C*H), 133.8 (Ar*C*Br), 142.9 (Furyl-2-*C*H), 143.6 (Furyl-5-*C*H), 158.2 (1C, q, *J* = 35.9, *C*CF_3), 160.5 (Ar*C*); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.8 (3F, s, C*F*$_3$); m/z (EI) 526+528 (1:1, 4%, M^+), 480+482 (1:1, 46%, M^+-NO_2); HRMS $C_{22}H_{18}(^{79}Br)F_3N_2O_5$ calcd. 526.0346, found 526.0338; Anal. calcd. for $C_{22}H_{18}BrF_3N_2O_5$: C, 50.11; H, 3.44; N, 5.31; found: C, 49.96; H, 3.32; N, 5.27%.

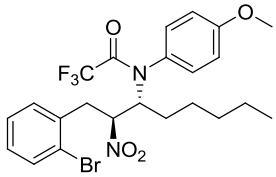
_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(thiophen-2-yl)propyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232d)



232d

Prepared using general procedure H. Crude *β*-nitroamine **230d** (4.39 mmol) afforded crude *β*-nitroacetamide **232d** as a brown oil. Purification by flash column chromatography (50% CH_2Cl_2/Pet. ether followed by 20% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232d** as a white solid (1.76 g, 74%, *anti*:*syn* >20:1); mp 126-128 °C; R_f 0.25 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3082-2841 (C-H), 1698 (C=O), 1557 (N-O), 1510 (C=C), 1254 (N-O), 1207 (C-O), 1180 (C-F), 1156 (C-F), 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.54 (1H, dd, *J* = 14.2, 11.6, C*H*$_2$), 3.77 (1H, dd, *J* = 14.3, 3.6, C*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 5.81 (1H, br m, C*H*NO_2), 6.23 (1H, br s, C*H*NPMP), 6.69 (1H, br s, Ar*H*), 6.78 (2H, m, thiophenyl-5-*H* + Ar*H*), 6.86 (1H, dd, *J* = 5.0, 3.7, thiophenyl-4-*H*), 6.93 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 7.15-7.19 (2H, m, Ar*H*), 7.26 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.31 (1H, dd, *J* = 5.1, 0.9, thiophenyl-3-*H*), 7.34 (1H, br d, *J* = 8.0, Ar*H*), 7.61 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.5 (*C*H_2), 55.6 (O*C*H_3), 61.9 (*C*HNPMP), 88.9 (*C*HNO_2), 114.1 (Ar*C*H), 114.7 (Ar*C*H), 116.2 (1C, q, *J* = 288.5, *C*F_3), 124.2 (Ar*C*CH_2), 126.9 (thiophenyl-4-*C*H), 128.0 (thiophenyl-3-*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*N), 129.8 (thiophenyl-5-*C*H), 129.9 (Ar*C*H), 130.5 (Ar*C*H), 131.2 (Ar*C*H), 131.5 (Ar*C*H), 133.3 (Ar*C*H), 133.7 (Ar*C*Br), 134.2 (thiophenyl-2-*C*), 158.1 (1C, q, *J* = 36.1, *C*F_3), 160.6 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.8 (3F, s, C*F*$_3$); m/z (CI) 543+545 (1:1, 3%, M^++H), 496+498 (1:1, 5%, M^+-NO_2), 324+326 (1:1, 86%, M^+-PMPNTFA); HRMS $C_{22}H_{19}(^{79}Br)F_3N_2O_4S$ calcd. 543.0201, found 543.0185; Anal. calcd. for $C_{22}H_{18}BrF_3N_2O_4S$: C, 48.63; H, 3.34; N, 5.16; found: C, 48.32; H, 3.19; N, 4.95%.

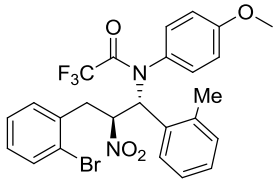
_N_-((2_S_*,3_R_*)-1-(2-Bromophenyl)-2-nitrooctan-3-yl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232e)



232e

Prepared using general procedure I. Crude *β*-nitroamine **230e** (4.24 mmol) afforded crude *β*-nitroacetamide **232e** as a brown oil. Purification by flash column chromatography (60% CH_2Cl_2/Pet. ether followed by 20% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232e** as a white solid (1.91 g, 85%, *anti*:*syn* >20:1); mp 88-90 °C; R_f 0.33 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3059-2862 (C-H), 1698 (C=O), 1554 (N-O), 1511 (C=C), 1255 (N-O), 1205, 1182 (C-F), 1171 (C-F), 1154 (C-F), 1028 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0, CH_2CH_3), 1.20-1.53 (7H, m, $(CH_2)_4CH_3$), 1.74-1.79 (1H, m, $(CH_2)_4CH_3$), 3.42 (1H, dd, *J* = 14.5, 11.4, $ArCH_2$), 3.55 (1H, dd, *J* = 14.5, 3.7, $ArCH_2$), 3.87 (3H, s, OCH_3), 4.93 (1H, br s, CHNPMP), 5.21 (1H, td, *J* = 10.1, 3.4, $CHNO_2$), 6.96 (2H, dm, *J* = 9.2, Ar*H*), 7.13 (1H, dd, *J* = 7.6, 1.5, Ar*H*), 7.16 (1H, td, *J* = 7.7, 1.8, Ar*H*), 7.21 (1H, br m, Ar*H*), 7.25 (1H, td, *J* = 7.4, 1.3, Ar*H*), 7.38 (1H, br d, *J* = 7.6, Ar*H*), 7.58 (1H, dd, *J* = 7.9, 1.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 22.5 (CH_2CH_3), 26.4 ($CH_2CH_2CH_3$), 28.0 ($CHCH_2CH_2$), 31.3 ($CHCH_2$), 38.1 (CH_2CHNO_2), 55.7 (OCH_3), 62.5 (CHNPMP), 89.2 ($CHNO_2$), 114.6 (ArCH), 116.3 (1C, q, *J* = 288.7, CF_3), 124.2 ($ArCCH_2$), 128.2 (ArCN), 128.2 (ArCH), 129.7 (ArCH), 130.6 (ArCH), 130.8 (ArCH), 131.5 (ArCH), 133.3 (ArCH), 134.1 (ArCBr), 158.7 (1C, q, *J* = 35.2, CCF_3), 160.5 (ArCO); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.4 (3F, s, CF_3); m/z (EI) 530+532 (1:1, 18%, M^+), 265+267 (1:1, M^+-(PMPNTFA+NO_2)), 219 (55%, $PMPN^+TFA$); HRMS $C_{23}H_{26}(^{79}Br)F_3N_2O_4$ calcd. 530.1023, found 530.1024; Anal. calcd. for $C_{23}H_{26}BrF_3N_2O_4$: C, 51.99; H, 4.93; N, 5.27; found: C, 52.05; H, 4.91; N, 5.21%.

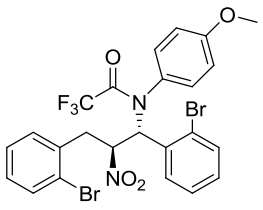
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(_o_-tolyl)propyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232h)



232h

Prepared using general procedure H. Crude *β*-nitroamine **230h** (5.10 mmol) afforded crude *β*-nitroacetamide **232h** as a yellow oil. Purification by flash column chromatography (35% CH_2Cl_2/Pet. ether) yielded *β*-nitroacetamide **232h** as a white solid (2.28 g, 81%, *anti*:*syn* >20:1); mp 154-156 °C; R_f 0.34 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3067-2841 (C-H), 1697 (C=O), 1557 (N-O), 1511 (C=C), 1255 (N-O), 1207 (C-O), 1180 (C-F), 1167 (C-F), 1155 (C-F), 1032 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.45 (3H, s, ArCH_3), 3.67 (1H, dd, *J* = 14.3, 11.6, CH_2), 3.80 (3H, s, OCH_3), 3.80 (1H, dd, *J* = 14.2, 3.9, CH_2), 5.64 (1H, td, *J* = 10.8, 2.6, $CHNO_2$), 6.00 (1H, d, *J* = 6.5, Ar*H*), 6.51 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.55 (1H, br s, Ar*H*), 6.84 (1H, t, *J* = 7.4, Ar*H*), 6.85 (1H, br m, C*H*NTFA), 6.92 (1H, dd, *J* = 8.7, 3.0, Ar*H*), 7.14-7.21 (4H, m, Ar*H*), 7.27 (1H, td, *J* = 7.4, 1,2, Ar*H*), 7.54 (1H, br d, *J* = 7.9, Ar*H*), 7.63 (1H, dd, *J* = 8.0, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.8 (ArCCH_3), 38.7 (CH_2), 55.6 (OCH_3), 59.0 (*C*HNTFA), 87.2 ($CHNO_2$), 113.5 (Ar*C*H), 114.2 (Ar*C*H), 116.4 (1C, q, *J* = 288.6, CF_3), 124.0 (ArCCH_2), 125.9 (Ar*C*H), 126.8 (Ar*C*N), 128.2 (Ar*C*H), 128.5 (Ar*C*H), 129.4 (Ar*C*H), 129.9 (Ar*C*H), 130.8 (Ar*C*H), 130.8 (ArCCH_3), 131.1 (Ar*C*H), 131.9 (Ar*C*H), 132.7 (Ar*C*H), 133.2 (Ar*C*H), 134.0 (Ar*C*Br), 138.0 (Ar*C*CNTFA), 158.4 (1C, q, *J* = 35.7, CCF_3), 160.4 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.3 (3F, s, CF_3); m/z (EI) 551+553 (1:1, 27%, M^++H), 550+552 (1:1, 100%, M^+), 504+506 (1:1, 19%, M^+-NO_2); HRMS $C_{25}H_{22}(^{79}Br)F_3N_2O_4$ calcd. 550.0710, found 550.0714; Anal. calcd. for $C_{25}H_{22}BrF_3N_2O_4$: C, 54.46; H, 4.02; N, 5.08; found: C, 54.45; H, 3.93; N, 5.06%.

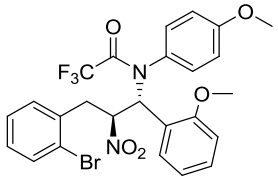
_N_-((1_R_*,2_S_*)-1,3-Bis(2-bromophenyl)-2-nitropropyl)-_N_-(4-methoxyphenyl) -2,2,2-trifluoroacetamide (232i)



232i

Prepared using general procedure I. Crude *β*-nitroamine **230i** (4.39 mmol) afforded crude *β*-nitroacetamide **232i** as a yellow oil. Purification by flash column chromatography (40% CH_2Cl_2/Pet. ether) and subsequent recrystallisation from toluene/Pet. ether yielded pure *β*-nitroacetamide **232i** as a white solid (2.24 g, 83%, *anti*:*syn* >20:1); mp 197-198 °C; R_f 0.34 (40% CH_2Cl_2/Pet. ether); IR υ_{max} (neat) 3067-2840 (C-H), 1702 (C=O), 1556 (N-O), 1511 (C=C), 1256 (N-O), 1207 (C-O), 1181 (C-F), 1167 (C-F), 1156 (C-F), 1030 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.71 (1H, dd, *J* = 14.3, 11.6, C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 3.79 (1H, dd, *J* = 14.3, 3.9, C*H*$_2$), 5.64 (1H, td, *J* = 11.3, 3.8, C*H*NO_2), 6.22 (1H, d, *J* = 7.7, Ar*H*), 6.50 (1H, dd, *J* = 8.9, 2.9, Ar*H*), 6.71 (1H, d, *J* = 7.7, Ar*H*), 6.90 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.97 (1H, m, Ar*H*), 7.00 (1H, d, *J* = 11.0, C*H*NPMP), 7.13 (1H, td, *J* = 7.7, 1.4, Ar*H*), 7.16 (1H, dd, *J* = 7.5, 1.6, Ar*H*), 7.20 (1H, td, *J* = 7.7, 1.7, Ar*H*), 7.28 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.53 (1H, dd, *J* = 8.7, 2.5, Ar*H*), 7.63 (2H, dt, *J* = 8.0, 1.6, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.7 (*C*H_2), 55.6 (O*C*H_3), 61.9 (*C*HNPMP), 87.2 (*C*HNO_2), 113.6 (Ar*C*H), 114.4 (Ar*C*H), 116.4 (1C, q, *J* = 288.5, *C*F_3), 123.9 (Ar*C*CH_2), 126.1 (Ar*C*CHN), 127.0 (Ar*C*N), 127.4 (Ar*C*H), 128.5 (Ar*C*H), 129.7 (Ar*C*H), 130.0 (Ar*C*H), 130.8 (Ar*C*H), 130.9 (Ar*C*H), 131.9 (Ar*C*H), 132.2 (Ar*C*H), 132.3 (Ar*C*Br), 133.2 (Ar*C*H), 133.7 (Ar*C*H), 133.9 (Ar*C*Br), 158.1 (1C, q, *J* = 35.9, *C*CF_3), 160.4 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.4 (3F, s, C*F*$_3$); m/z (EI) 618+616+614 (1:2:1, 15%, M^+), 535+537 (1:1,4%, M^+-Br), 353+351+349 (1:2:1, 45%, M^+-(NO_2+PMPNTFA)); HRMS $C_{24}H_{19}(^{79}Br)_2F_3N_2O_4$ calcd. 613.9658, found 613.9667; Anal. calcd. for $C_{24}H_{19}Br_2F_3N_2O_4$: C, 46.78; H, 3.11; N, 4.55; found: C, 47.02; H, 3.00; N, 4.48%.

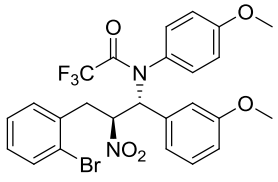
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(2-methoxyphenyl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232j)



232j

Prepared using general procedure H. Crude *β*-nitroamine **230j** (4.80 mmol) afforded crude *β*-nitroacetamide **232j** as a brown oil. Purification by flash column chromatography (35% Et_2O/Pet. ether followed by 50% CH_2Cl_2/Pet. ether) yielded pure *β*-nitroacetamide **232j** as a white solid (2.25 g, 83%, *anti*:*syn* >20:1); mp 130-132 °C; R_f 0.35 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3071-2841 (C-H), 1699 (C=O), 1556 (N-O), 1511 (C=C), 1252 (N-O), 1206 (C-O), 1180 (C-F), 1166 (C-F), 1154 (C-F), 1026 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.65 (1H, dd, *J* = 14.3, 11.7, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 3.79 (1H, dd, *J* = 14.4, 3.9, C*H*$_2$), 3.81 (3H, br s, OC*H*$_3$), 5.69 (1H, td, *J* = 11.2, 3.1, C*H*NO_2), 6.14 (1H, d, *J* = 8.2, Ar*H*), 6.52 (1H, dd, *J* = 8.9, 2.9, Ar*H*), 6.67 (1H, t, *J* = 7.5, Ar*H*), 6.77 (1H, br d, *J* = 5.9, Ar*H*), 6.86 (1H, d, *J* = 8.2, Ar*H*), 6.89 (1H, dd, *J* = 8.7, 2.9, Ar*H*), 6.96 (1H, br d, *J* = 11.2, C*H*NTFA), 7.16 (1H, dd, *J* = 7.5, 1.7, Ar*H*), 7.18 (1H, td, *J* = 7.7, 1.7, Ar*H*), 7.24 (1H, m, Ar*H*), 7.26 (1H, td, *J* = 7.4, 1.1, Ar*H*), 7.50 (1H, dd, *J* = 8.7, 2.2, Ar*H*), 7.62 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.8 (*C*H_2), 55.5 (O*C*H_3), 55.8 (O*C*H_3), 57.4 (*C*HNTFA), 86.8 (*C*HNO_2), 110.9 (Ar*C*H), 113.4 (Ar*C*H), 114.0 (Ar*C*H), 116.5 (1C, q, *J* = 288.7, *C*F_3), 120.4 (Ar*C*H), 121.1 (Ar*C*CNTFA), 124.0 (Ar*C*CH_2), 127.5 (Ar*C*N), 128.4 (Ar*C*H), 129.2 (Ar*C*H), 129.8 (Ar*C*H), 130.8 (Ar*C*H), 130.9 (Ar*C*H), 131.9 (Ar*C*H), 132.1 (Ar*C*H), 133.2 (Ar*C*H), 134.2 (Ar*C*Br), 157.8 (Ar*C*O), 158.1 (1C, q, *J* = 35.3, *C*CF_3), 160.2 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.3 (3F, s, C*F*$_3$); m/z (EI) 566+568 (1:1, 5%, M^+); HRMS $C_{25}H_{22}(^{79}Br)F_3N_2O_5$ calcd. 566.0659, found 566.0642; Anal. calcd. for $C_{25}H_{22}BrF_3N_2O_5$: C, 52.92; H, 3.91; N, 4.94; found: C, 52.81; H, 3.83; N, 4.90%.

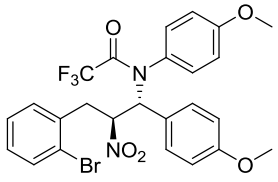
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(3-methoxyphenyl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232k)



232k

Prepared using general procedure H. Crude *β*-nitroamine **230k** (0.776 mmol) afforded crude *β*-nitroacetamide **232k** as a dark yellow oil. Purification by flash column chromatography (45% CH_2Cl_2/Pet. ether followed by 40% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232k** as a white solid (387 mg, 88%, *anti*:*syn* >20:1); mp 132-133 °C; R_f 0.50 (40% Et_2O/Pet. ether); IR υ_{max} (neat) 3056-2839 (C-H), 1698 (C=O), 1557 (N-O), 1511 (C=C), 1255 (N-O), 1208 (C-O), 1181 (C-F), 1168 (C-F), 1156 (C-F), 1036 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 3.78 (1H, dd, *J* = 14.4, 3.7, C*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.73 (1H, td, *J* = 11.1, 3.3, C*H*NO_2), 6.26 (1H, br d, *J* = 10.1, C*H*NPMP), 6.35 (1H, br d, *J* = 7.8, Ar*H*), 6.63-6.68 (3H, m, Ar*H*), 6.85 (1H, ddd, *J* = 8.3, 2.3, 0.9, Ar*H*), 6.92 (1H, dd, *J* = 8.7, 2.9, Ar*H*), 7.13 (1H, t, *J* = 8.2, Ar*H*), 7.17-7.21 (2H, m, Ar*H*), 7.27 (1H, td, *J* = 7.5, Ar*H*), 7.41 (1H, br d, *J* = 8.0, Ar*H*), 7.61-7.63 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.7 (*C*H_2), 55.4 (O*C*H_3), 55.6 (*C*H_2), 64.7 (*C*HNPMP), 87.2 (*C*HNO_2), 113.8 (Ar*C*H), 114.4 (Ar*C*H), 114.9 (Ar*C*H), 115.6 (Ar*C*H), 116.3 (1C, q, *J* = 288.7, *C*F_3), 121.8 (Ar*C*H), 124.1 (Ar*C*CH_2), 127.7 (Ar*C*CHN), 128.4 (Ar*C*H), 129.8 (Ar*C*H), 129.9 (Ar*C*H), 130.8 (Ar*C*H), 131.6 (Ar*C*H), 132.4 (Ar*C*H), 133.3 (Ar*C*H), 133.9 (Ar*C*Br), 134.2 (Ar*C*N), 158.3 (1C, q, *J* = 35.8, *C*CF_3), 159.7 (Ar*C*O), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.5 (3F, s, C*F*$_3$); m/z (EI) 566+568 (1:1, 15%, M^+), 367 (30%, M^+-C_8H_9BrO), 302+304 (1:1, 52%, M^+-(PMPNTFA+NO_2)), 219 (87%, PMPN^+TFA); HRMS $C_{25}H_{22}(^{79}Br)F_3N_2O_5$ calcd. 566.0659, found 566.0645; Anal. calcd. for $C_{25}H_{22}BrF_3N_2O_5$: C, 52.92; H, 3.91; N, 4.94; found: C, 52.95; H, 3.82; N, 4.88%.

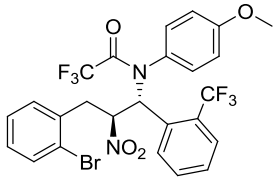
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(4-methoxyphenyl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232l)



232l

Prepared using general procedure H. Crude *β*-nitroamine **230l** (4.79 mmol) afforded crude *β*-nitroacetamide **232l** as a brown oil. Purification by flash column chromatography (60% CH_2Cl_2/Pet. ether followed by 30% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232l** as a white solid (2.23 g, 82%, *anti*:*syn* >20:1); mp 114-116 °C; R_f 0.36 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3007-2841 (C-H), 1698 (C=O), 1557 (N-O), 1511 (C=C), 1256 (N-O), 1207 (C-O), 1177 (C-F), 1169 (C-F), 1156 (C-F), 1031 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (1H, dd, *J* = 14.3, 11.6, C*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 3.77 (1H, dd, *J* = 14.3, 3.7, C*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.70 (1H, br m, C*H*NO_2), 6.26 (1H, br s, C*H*NPMP), 6.31 (1H, br s, Ar*H*), 6.67 (1H, dd, *J* = 8.6, 2.2, Ar*H*), 6.74 (2H, d, *J* = 8.8, Ar*H*), 6.92 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.98 (2H, br d, *J* = 8.0, Ar*H*), 7.17-7.19 (2H, m, Ar*H*), 7.25-7.28 (1H, m, Ar*H*), 7.42 (1H, br d, *J* = 7.6, Ar*H*), 7.61 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.6 (*C*H_2), 55.4 (OCH_3), 55.6 (OCH_3), 64.5 (*C*HNPMP), 87.5 (*C*HNO_2), 113.8 (Ar*C*H), 114.1 (Ar*C*H), 114.4 (Ar*C*H), 116.4 (1C, q, *J* = 288.7, *C*F_3), 124.1 (Ar*C*CH_2), 124.7 (Ar*C*CNPMP), 127.7 (Ar*C*N), 128.4 (Ar*C*H), 129.8 (Ar*C*H), 130.8 (Ar*C*H), 130.9 (Ar*C*H), 131.7 (Ar*C*H), 132.6 (Ar*C*H), 133.3 (Ar*C*H), 134.0 (Ar*C*Br), 158.2 (1C, q, *J* = 35.6, *C*CF_3), 160.4 (Ar*C*O), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.5 (3F, s, C*F*$_3$); m/z (EI) 566+568 (4%, M^+), 520+522 (12%, M^+-NO_2), 348+350 (M^+-PMPNHTFA), 302+304 (M^+-(NO_2+PMPNHTFA); HRMS $C_{25}H_{22}(^{79}Br)F_3N_2O_5$ calcd. 566.0659, found 566.0638; Anal. calcd. for $C_{25}H_{22}BrF_3N_2O_5$: C, 52.92; H, 3.91; N, 4.94; found: C, 53.01; H, 3.84; N, 4.76%.

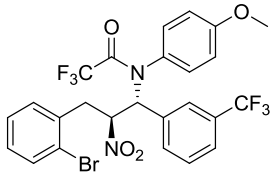
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(2-(trifluoromethyl)phenyl)propyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232m)



232m

Prepared using general procedure I. Crude *β*-nitroamine **230m** (3.24 mmol) afforded crude *β*-nitroacetamide **232m** as a brown oil. Purification by flash column chromatography (40% CH_2Cl_2/Pet. ether followed by 30% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232m** as a white solid (1.33 g, 68%, *anti*:*syn* = 9:1). Subsequent recrystallisation from toluene/Pet. ether gave *β*-nitroacetamide **232m** as a single *anti* diastereomer (1.18 g, 60%); mp 153-154 °C; R_f 0.33 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3057-2843 (C-H), 1705 (C=O), 1557 (N-O), 1512 (C=C), 1313, 1257 (N-O), 1210 (C-O), 1182 (C-F), 1159 (C-O), 1125 (C-F), 1038 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.71 (1H, dd, *J* = 14.4, 11.6, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 3.80 (1H, dd, *J* = 14.3, 3.8, C*H*$_2$), 5.62 (1H, td, *J* = 11.1, 3.8, C*H*NO_2), 6.04 (1H, dd, *J* = 8.8, 2.0, Ar*H*), 6.46 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.67 (1H, d, *J* = 7.9, Ar*H*), 6.95 (1H, dd, *J* = 8.7, 3.0, Ar*H*), 7.14 (1H, d, *J* = 10.5, C*H*NPMP), 7.15 (2H, dd, *J* = 7.5, 1.7, Ar*H*), 7.20 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.27 (1H, td, *J* = 7.5, 1.2, Ar*H*), 7.38 (1H, t, *J* = 7.7, Ar*H*), 7.63 (1H, dd, *J* = 7.9, 1.1, Ar*H*), 7.64 (1H, dd, *J* = 8.7, 2.6, Ar*H*), 7.74 (1H, d, *J* = 7.6, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.9 (*C*H_2), 55.6 (O*C*H_3), 57.5 (*C*HNPMP), 87.7 (*C*HNO_2), 113.7 (Ar*C*H), 114.3 (Ar*C*H), 116.3 (1C, q, *J* = 288.4, CO*C*F_3), 123.8 (1C, q, *J* = 274.1, Ar*C*F_3), 123.9 (Ar*C*CH_2), 126.6 (Ar*C*N), 126.9 (1C, q, *J* = 5.9, Ar*C*H), 128.6 (Ar*C*H), 129.7 (Ar*C*H), 130.0 (Ar*C*H), 130.2 (1C, q, *J* = 30.4, Ar*C*CF_3), 130.4 (Ar*C*CHN), 130.4 (Ar*C*H), 131.2 (Ar*C*H), 131.4 (Ar*C*H), 132.0 (Ar*C*H), 132.6 (Ar*C*H), 133.2 (Ar*C*H), 133.8 (Ar*C*N), 158.1 (1C, q, *J* = 35.9, *C*CF_3), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$), -60.2 (3F, s, C*F*$_3$); m/z (EI) 604+606 (1:1, 32%, M^+), 339+341 (1:1, 85%, M^+-(PMPNHTFA+NO_2)), 261 (38%, M^+-(PMPNHTFA+Br+NO_2)), 218 (100%, PMPN^+TFA); HRMS $C_{25}H_{19}(^{79}Br)F_6N_2O_4$ calcd. 604.0427, found 604.0411; Anal. calcd. for $C_{25}H_{19}BrF_6N_2O_4$: C, 49.60; H, 3.16; N, 4.63; found: C, 49.24; H, 3.03; N, 4.57%.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-nitro-1-(3-(trifluoromethyl)phenyl)propyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232n)

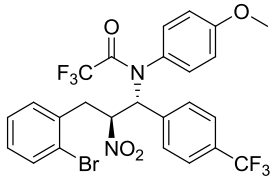


232n

Prepared using general procedure H. Crude *β*-nitroamine **230n** (0.623 mmol) afforded crude *β*-nitroacetamide **232n** as a brown oil. Purification by flash column chromatography (40% CH_2Cl_2/Pet. ether followed by 30% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide

232n as an off-white solid (344 mg, 91%, *anti*:*syn* >20:1); mp 57-60 °C; R_f 0.53 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3061-2841 (C-H), 1700 (C=O), 1557 (N-O), 1511 (C=C), 1328, 1257, 1209 (C-F), 1180 (C-F), 1164 (C-F), 1127 (C-F), 1076, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$), 3.81 (1H, dd, *J* = 14.2, 3.6, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.75 (1H, td, *J* = 11.1, 3.4, C*H*NO_2), 6.26 (1H, d, *J* = 8.0, Ar*H*), 6.36 (1H, d, *J* = 10.7, C*H*NHPMP), 6.66 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.96 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 7.16-7.22 (2H, m, Ar*H*), 7.23 (1H, s, Ar*H*), 7.28 (1H, td, *J* = 7.5, 1.3, Ar*H*), 7.33 (1H, d, *J* = 7.9, Ar*H*), 7.39 (1H, d, *J* = 7.8, Ar*H*), 7.42 (1H, d, *J* = 8.4, Ar*H*), 7.59 (1H, d, *J* = 7.7, Ar*H*), 7.63 (1H, dd, *J* = 7.9, 1.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.6 (*C*H_2), 55.7 (O*C*H_3), 64.3 (*C*HNHPMP), 87.2 (*C*HNO_2), 114.4 (Ar*C*H), 114.5 (Ar*C*H), 116.2 (1C, q, *J* = 288.6, CO*C*F_3), 123.5 (1C, q, *J* = 272.6, Ar*C*F_3), 124.1 (Ar*C*CH_2), 126.5 (1C, q, *J* = 3.7, Ar*C*H), 126.7 (1C, q, *J* = 3.6, Ar*C*H), 127.3 (Ar*C*N), 128.5 (Ar*C*H), 129.5 (Ar*C*H), 130.0 (Ar*C*H), 130.8 (Ar*C*H), 131.2 (1C, q, *J* = 32.7, Ar*C*CF_3), 131.6 (Ar*C*H), 132.3 (Ar*C*H), 133.0 (Ar*C*H), 133.3 (Ar*C*H), 133.6 (Ar*C*Br), 133.7 (Ar*C*CHNHPMP), 158.4 (1C, q, *J* = 36.0, *C*CF_3), 160.8 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$), -63.2 (3F, s, C*F*$_3$); m/z (EI) 604+606 (1:1, 6%, M^+), 339+341 (1:1, 10%, M^+-(PMPNTFA+NO_2); HRMS $C_{25}H_{19}(^{79}Br)F_6N_2O_4$ calcd. 604.0427, found 604.0424; Anal. calcd. for $C_{25}H_{19}BrF_6N_2O_4$: C, 49.60; H, 3.16; N, 4.63; found: C, 49.65; H, 3.10; N, 4.55%.

N-((1*R**,2*S**)-3-(2-Bromophenyl)-2-nitro-1-(4-(trifluoromethyl)phenyl)propyl)-*N*-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232o)

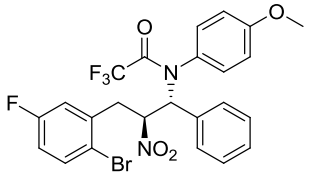


232o

Prepared using general procedure H. Crude *β*-nitroamine **230o** (0.925 mmol) afforded crude *β*-nitroacetamide **232o** as a brown oil. Purification by flash column chromatography (35% CH_2Cl_2/Pet. ether) yielded pure *β*-nitroacetamide **232o** as a white solid (507 g, 91%, *anti*:*syn* >20:1); mp 126-128 °C; R_f 0.20 (30% CH_2Cl_2/Pet. ether); IR υ_{max} (neat) 3060-2843 (C-H), 1702 (C=O), 1558 (N-O), 1511 (C=C), 1325 (C-F), 1256 (N-O), 1211 (C-O), 1180 (C-F), 1167 (C-F), 1124 (C-F), 1069, 1027 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (1H, dd, *J* = 14.3, 11.4, C*H*$_2$), 3.82 (1H, dd, *J* = 14.4, 3.7, C*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 5.82 (1H, td, *J* = 11.1, 3.4, C*H*NO_2), 6.27 (1H, br d, *J* = 10.5, C*H*NPMP), 6.36 (1H, br d, *J*

= 7.2, Ar*H*), 6.70 (1H, dd, *J* = 8.8, 2.7, Ar*H*), 6.94 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 7.17 (1H, dd, *J* = 7.5, 1.7, Ar*H*), 7.20 (1H, td, *J* = 7.6, 1.9, Ar*H*), 7.24-7.27 (2H, m, Ar*H*), 7.28 (1H, td, *J* = 7.5, 1.3, Ar*H*), 7.38 (1H, br d, *J* = 7.9, Ar*H*), 7.52 (2H, d, *J* = 8.2, Ar*H*), 7.63 (1H, dd, *J* = 7.9, 1.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.7 (*C*H_2), 55.7 (O*C*H_3), 64.8 (*C*HNHPMP), 87.1 (*C*HNO_2), 114.2 (Ar*C*H), 114.6 (Ar*C*H), 116.2 (1C, q, *J* = 288.6, CO*C*F_3), 123.7 (1C, q, *J* = 272.5, Ar*C*F_3), 124.1 (Ar*C*CH_2), 125.9 (1C, q, *J* = 3.7, Ar*C*H), 127.7 (Ar*C*N), 128.5 (Ar*C*H), 130.0 (Ar*C*H), 130.0 (Ar*C*H), 130.8 (Ar*C*H), 131.6 (Ar*C*H), 131.9 (1C, q, *J* = 32.8, Ar*C*CF_3), 132.0 (Ar*C*H), 133.3 (Ar*C*H), 133.6 (Ar*C*Br), 136.7 (Ar*C*CHN), 158.4 (1C, q, *J* = 36.1, *C*OCF_3), 160.7 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$), -63.3 (3F, s, C*F*$_3$); m/z (EI) 604+606 (1:1, 13%, M^+), 339+441 (1:1, 12%, M^+-(PMPNHTFA+NO_2)), 219 (97%, M^+-PMPN^+TFA); HRMS $C_{25}H_{19}(^{79}Br)F_6N_2O_4$ calcd. 604.0427, found 604.0424; Anal. calcd. for $C_{25}H_{19}BrF_6N_2O_4$: C, 49.60; H, 3.16; N, 4.63; found: C, 49.80; H, 3.16; N, 4.54%.

_N_-((1_R_*,2_S_*)-3-(2-Bromo-5-fluorophenyl)-2-nitro-1-phenylpropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232p)

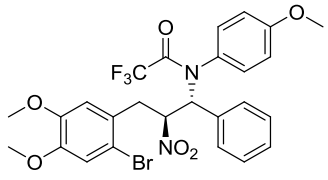


232p

Prepared using general procedure H. Crude *β*-nitroamine **230p** (0.480 mmol) afforded crude *β*-nitroacetamide **232p** as a yellow oil. Purification by flash column chromatography (40% CH_2Cl_2/Pet. ether followed by 25% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232p** as a white solid (219 mg, 82%, *anti*:*syn* >20:1); mp 118-120 °C; R_f 0.51 (25% Et_2O/Pet. ether); IR υ_{max} (neat) 3069-2842 (C-H), 1698 (C=O), 1557 (N-O), 1511 (C=C), 1474, 1255 (N-O), 1208 (C-O), 1181 (C-F), 1155 (C-F), 1032 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.58 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$), 3.74 (1H, dd, *J* = 14.4, 3.7, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.78 (1H, td, *J* = 11.2, 3.5, C*H*NO_2), 6.24 (1H, br d, *J* = 10.7, C*H*NPMP), 6.31 (1H, br d, *J* = 8.2, Ar*H*), 6.65 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.93 (2H, td, *J* = 8.4, 3.1, Ar*H*), 6.94 (1H, d, *J* = 8.2, Ar*H*), 7.09 (2H, d, *J* = 7.4, Ar*H*), 7.24 (2H, t, *J* = 7.5, Ar*H*), 7.30-7.36 (2H, m, Ar*H*), 7.56-7.60 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.6 (*C*H_2), 55.6 (O*C*H_3), 65.1 (*C*HNPMP), 87.0 (*C*HNO_2), 113.9 (Ar*C*H), 114.4 (Ar*C*H), 116.3 (1C, q, *J* = 288.5, *C*F_3), 117.2 (1C, d, *J* = 22.2, Ar*C*H), 118.3 (1C, d, *J* = 3.2, Ar*C*CH_2),

118.7 (1C, d, *J* = 23.1, Ar*C*H), 127.7 (Ar*C*N), 128.9 (Ar*C*H), 129.6 (Ar*C*H), 129.9 (Ar*C*H), 130.7 (Ar*C*H), 132.3 (Ar*C*H), 132.6 (Ar*C*CHN), 134.5 (1C, d, *J* = 7.9, Ar*C*H), 135.9 (1C, d, *J* = 7.6, Ar*C*Br), 158.3 (1C, q, *J* = 35.8, *C*CF_3), 160.5 (Ar*C*O), 162.1 (1C, d, *J* = 248.8, Ar*C*F); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.5 (1F, m, CF_3), -67.5 (3F, s, CF_3); m/z (EI) 554+556 (1:1, 7%, M^+), 335+337 (1:1, 9%, M^+-PMPNTFA); HRMS $C_{24}H_{19}(^{79}Br)F_4N_2O_4$ calcd. 554.0459, found 554.0465; Anal. calcd. for $C_{24}H_{19}BrF_4N_2O_4$: C, 51.91; H, 3.45; N, 5.04; found: C, 52.04; H, 3.39; N, 5.00%.

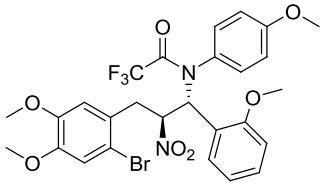
_N_-((1_R_*,2_S_*)-3-(2-Bromo-4,5-dimethoxyphenyl)-2-nitro-1-phenylpropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232q)



232q

Prepared using general procedure H. Crude *β*-nitroamine **230q** (0.472 mmol) afforded crude *β*-nitroacetamide **232q** as a yellow foam. Purification by flash column chromatography (50% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232q** as an off-white solid (248 mg, 88%, *anti*:*syn* >20:1); mp 72-75 °C; R_f 0.48 (50% Et_2O/Pet. ether); IR υ_{max} (neat) 3008-2842 (C-H), 1697 (C=O), 1556 (N-O), 1509 (C=C), 1258 (N-O), 1206 (C-O), 1180 (C-F), 1155 (C-F), 1032 (C-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$), 3.72 (1H, dd, *J* = 14.4, 3.8, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 5.71 (1H, td, *J* = 11.1, 3.5, C*H*NO_2), 6.26 (1H, br d, *J* = 8.0, Ar*H*), 6.31 (1H, br d, *J* = 11.0, C*H*NPMP), 6.63 (1H, m, Ar*H*), 6.64 (1H, s, Ar*H*), 6.92 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 7.05 (1H, s, Ar*H*), 7.06 (2H, m, Ar*H*), 7.23 (2H, t, *J* = 7.5, Ar*H*), 7.27-7.33 (1H, m, Ar*H*), 7.42 (1H, br d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.4 (*C*H_2), 55.6 (O*C*H_3), 56.2 (O*C*H_3), 56.3 (O*C*H_3), 64.7 (*C*HNPMP), 87.4 (*C*HNO_2), 113.8 (Ar*C*H), 113.9 (Ar*C*H), 114.0 (Ar*C*CH_2), 114.3 (Ar*C*H), 115.6 (Ar*C*H), 116.3 (1C, q, *J* = 288.7, *C*F_3), 125.6 (Ar*C*Br), 127.6 (Ar*C*N), 128.8 (Ar*C*H), 129.5 (Ar*C*H), 129.8 (Ar*C*H), 130.8 (Ar*C*H), 132.5 (Ar*C*H), 132.8 (Ar*C*CHN), 148.8 (Ar*C*O), 149.4 (Ar*C*O), 158.3 (1C, q, *J* = 35.7, *C*CF_3), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.5 (3F, s, CF_3); m/z (ES^+) 619+621 (1:1, 43%, M^++Na), 550+552 (86%, M^+-NO_2), 331+333 (1:1, 18%, M^+-PMPNTFA), 228+230 (75%, M^+-$C_{17}H_{14}F_3N_2O_4$); HRMS $C_{26}H_{24}(^{79}Br)F_3N_2O_6Na$ calcd. 619.0668, found 619.0672.

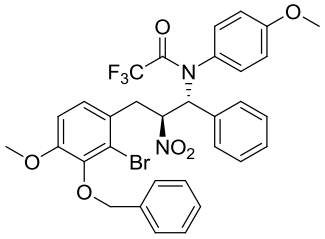
_N_-((1_R_,2_S_)-3-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-methoxyphenyl)-2-nitropropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232r)



232r

Prepared using general procedure H. Crude *β*-nitroamine **230r** (2.69 mmol) afforded crude *β*-nitroacetamide **232r** as a brown oil. Purification by flash column chromatography (70% CH_2Cl_2/Pet. ether followed by 60% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **232r** as a white solid (1.22 g, 72%, *anti*:*syn* >20:1); mp 81-83 °C; R_f 0.32 (50% Et_2O/Pet. ether); IR υ_{max} (neat) 3005-2842 (C-H), 1700 (C=O), 1556 (N-O), 1511 (C=C), 1496, 1255 (C-O), 1207 (C-F), 1181 (C-F), 1167 (C-F), 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.56 (1H, dd, *J* = 14.4, 11.5, C*H*$_2$), 3.73 (1H, dd, *J* = 14.4, 4.0, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 3.81 (6H, s, 2 x OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 5.65 (1H, td, *J* = 11.3, 3.8, C*H*NO_2), 6.14 (1H, d, *J* = 8.0, Ar*H*), 6.52 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.63 (1H, s, Ar*H*), 6.67 (1H, t, *J* = 7.4, Ar*H*), 6.76 (1H, d, *J* = 7.2, Ar*H*), 6.86 (1H, d, *J* = 8.9, Ar*H*), 6.89 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.95 (1H, d, *J* = 11.3, C*H*NHPMP), 7.05 (1H, s, OC*H*$_3$), 7.23-7.27 (1H, m, Ar*H*), 7.50 (1H, dd, *J* = 8.7, 2.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.6 (*C*H_2), 55.5 (O*C*H_3), 55.8 (O*C*H_3), 56.1 (O*C*H_3), 56.3 (O*C*H_3), 57.2 (*C*HNHPMP), 86.9 (*C*HNO_2), 110.9 (Ar*C*H), 113.4 (Ar*C*H), 113.9 (Ar*C*CH_2), 113.9 (Ar*C*H), 114.1 (Ar*C*H), 115.5 (Ar*C*H), 116.5 (1C, q, *J* = 288.6, *C*F_3), 120.4 (Ar*C*H), 121.1 (Ar*C*CHN), 125.9 (Ar*C*Br), 127.5 (Ar*C*N), 129.3 (Ar*C*H), 130.8 (Ar*C*H), 130.9 (Ar*C*H), 132.2 (Ar*C*H), 148.8 (Ar*C*O), 149.3 (Ar*C*O), 157.8 (Ar*C*O), 158.1 (1C, q, *J* = 35.3, *C*CF_3), 160.2 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.3 (3F, s, C*F*$_3$); m/z (EI) 626+628 (1:1, 20%, M^+), 361+363 (1:1, 100%, M^+-(PMPNHTFA+NO_2)), 229+231 (1:1, 98%, M^+-$C_{18}H_{17}F_3N_2O_5$); HRMS $C_{27}H_{26}(^{79}Br)F_3N_2O_7$ calcd. 626.0870, found 626.0847; Anal. calcd. for $C_{27}H_{26}BrF_3N_2O_7$: C, 51.69; H, 4.18; N, 4.46; found: C, 51.95; H, 4.14; N, 4.45%.

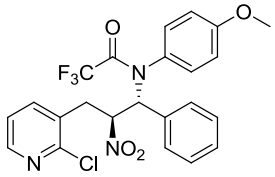
_N_-((1_R_*,2_S_*)-3-(3-(Benzyloxy)-2-bromo-4-methoxyphenyl)-2-nitro-1-phenylpropyl)-_N_-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232s)



232s

Prepared using general procedure H. Crude *β*-nitroamine **230s** (1.17 mmol) afforded crude *β*-nitroacetamide **232s** as a brown oil. Purification by flash column chromatography (60% CH_2Cl_2/Pet. ether) and subsequent recrystallisation from Et_2O/Pet. ether yielded pure *β*-nitroacetamide **232s** as a white solid (550 mg, 82%, *anti*:*syn* >20:1); mp 168-169 °C; R_f 0.33 (60% CH_2Cl_2/Pet. ether); IR υ_{max} (neat) 3064-2840 (C-H), 1699 (C=O), 1557 (N-O), 1511 (C=C), 1487, 1300, 1270, 1256, 1208, 1181, 1170, 1156, 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.56 (1H, dd, *J* = 14.4, 11.4, C*H*$_2$CHNO$_2$), 3.78 (1H, dd, *J* = 14.4, 3.8, C*H*$_2$CHNO$_2$), 3.82 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 5.06 (2H, s, OC*H*$_2$Ph), 5.71 (1H, td, *J* = 11.2, 3.5, C*H*NO$_2$), 6.22 (1H, d, *J* = 8.1, Ar*H*), 6.36 (1H, d, *J* = 10.5, C*H*NPMP), 6.61 (1H, dd, *J* = 8.8, Ar*H*), 6.83 (1H, d, *J* = 8.6, Ar*H*), 6.91 (1H, d, *J* = 8.5, Ar*H*), 6.92 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 7.06 (2H, d, *J* = 7.3, Ar*H*), 7.23 (2H, t, *J* = 7.5, Ar*H*), 7.29-7.44 (4H, m, Ar*H*), 7.46 (1H, d, *J* = 8.7, Ar*H*), 7.56-7.58 (2H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.6 (*C*H$_2$CHNO$_2$), 55.6 (OCH$_3$), 56.1 (OCH$_3$), 64.5 (*C*HNPMP), 74.8 (OCH$_2$Ph), 87.3 (C*H*NO$_2$), 111.7 (Ar*C*H), 113.7 (Ar*C*H), 114.3 (Ar*C*H), 116.4 (1C, q, *J* = 289.0, *C*F$_3$), 120.2 (Ar*C*CH$_2$CH), 126.5 (Ar*C*Br), 126.7 (Ar*C*H), 127.5 (Ar*C*CHN), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 129.6 (Ar*C*H), 129.7 (Ar*C*H), 130.9 (Ar*C*H), 132.5 (Ar*C*H), 132.9 (Ar*C*N), 137.1 (Ar*C*CH$_2$O), 145.5 (Ar*C*O), 153.6 (Ar*C*O), 158.3 (1C, q, *J* = 35.8, *C*CF$_3$), 160.4 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.4 (3F, s, C*F*$_3$); m/z (FAB$^+$) 695+697 (1:1, 8%, M^++Na), 549+551 (1:1, 5%, M^+-$C_8H_{10}O$); HRMS $C_{32}H_{28}(^{79}Br)F_3N_2O_6Na$ calcd. 695.0981, found 695.0968; Anal. calcd. for $C_{32}H_{28}BrF_3N_2O_6$: C, 57.07; H, 4.19; N, 4.16; found: C, 57.40; H, 4.20; N, 4.05%.

***N*-((1*R**,2*S**)-3-(2-Chloropyridin-3-yl)-2-nitro-1-phenylpropyl)-*N*-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232t)**



232t

Prepared using general procedure H. Crude *β*-nitroamine **230t** (0.99 mmol) afforded crude *β*-nitroacetamide **232t** as a brown oil. Purification by flash column chromatography (25% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **232t** as a white solid (290 mg, 59%, *anti*:*syn* >20:1); mp 53-55 °C; R_f 0.32 (25% EtOAc/Pet. ether); IR υ_{max} (neat) 3039-2851 (C-H), 1697 (C=O), 1557 (N-O), 1510 (C=C), 1411 (C=N), 1254, 1207, 1180 (C-F), 1155 (C-F) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (1H, dd, *J* = 14.5, 11.6, C*H*$_2$), 3.79 (1H, dd, *J* = 14.5, 3.6, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.70 (1H, td, *J* = 11.3, 3.5, C*H*NO_2), 6.20 (1H, d, *J* = 8.1, Ar*H*), 6.39 (1H, d, *J* = 10.0, C*H*Ph), 6.62 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.95 (1H, dd, *J* = 8.7, 2.9, Ar*H*), 7.05 (2H, d, *J* = 7.4, Ar*H*), 7.20-7.25 (3H, m, Ar*H*), 7.32 (1H, m, Ar*H*), 7.38 (1H, br dd, *J* = 8.7, 1.9, Ar*H*), 7.52 (1H, dd, *J* = 7.6, 1.9, Ar*H*), 8.37 (1H, dd, *J* = 4.7, 1.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.0 (*C*H_2), 55.5 (O*C*H_3), 64.0 (*C*HPh), 86.6 (*C*HNO_2), 113.7 (Ar*C*H), 114.4 (Ar*C*H), 116.2 (1C, q, *J* = 288.6, *C*F_3), 123.3 (Ar*C*H), 127.0 (Ar*C*CHN), 128.8 (Ar*C*H), 129.0 (Ar*C*CH_2), 129.4 (Ar*C*H), 129.8 (Ar*C*H), 130.4 (Ar*C*H), 132.3 (Ar*C*N), 132.5 (Ar*C*H), 140.3 (Ar*C*H), 149.5 (Ar*C*H), 150.8 (Ar*C*Cl), 158.4 (1C, q, *J* = 35.9, *C*CF_3), 160.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.5 (3F, s, C*F*$_3$); m/z (ES^+) 494 (80%, M^+), 447 (100%, M^+-NO_2), 230 (50%, $C_{14}H_{12}ClN$); HRMS $C_{23}H_{20}ClF_3N_3O_4$ calcd. 494.1094, found 494.1103.

4.4.6 Preparation of *β*-Aminoacetamides

General Procedure J

To a solution of *β*-nitroacetamide (1.00 mmol) in EtOAc (30.0 mL) and EtOH (40.0 mL) at 0 °C was added 6 M aq. HCl (250 mmol). The colourless solution was vigorously stirred and zinc dust (50.0 mmol) was added in three portions over 10 min. The grey suspension was removed from the cold bath and allowed to warm to rt over 2 h to give a colourless solution. Zinc dust (25.0 mmol) was added in one portion and the resultant grey suspension

stirred at room temperature for a further 1 h. The EtOH and EtOAc were removed *in vacuo* and the resultant aqueous solution was neutralised by the addition of $NaHCO_{3(s)}$ and extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with 2M HCl (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in EtOH (40.0 mL), 6 M $HCl_{(aq)}$ (20.0 mmol) was added and the mixture stirred at rt for 1 h before removal of the EtOH *in vacuo*. To the residue was added H_2O (40 mL) and the product was extracted into EtOAc (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude *β*-aminoacetamide which was purified by column chromatography.

General Procedure K

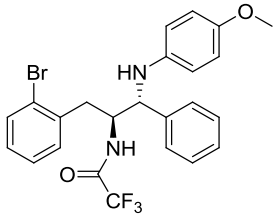
To a solution of *β*-aminohydroxylamine (1.00 mmol) in toluene (20.0 mL) at 0 °C was added dropwise $LiAlH_4$ (2 M in THF, 5.00 mmol). The reaction was stirred at 0 °C fro 1 h before being allowed to warm to rt and stirred until the reaction was complete by TLC analysis (1-3 h). The mixture was cooled to 0 °C before being quenched by the careful dropwise addition of ^{i}PrOH (0.35 mL per mmol $LiAlH_4$ = 1.8 mL) and brine (0.10 mL per mmol $LiAlH_4$ = 0.50 mL). The mixture was dried ($MgSO_4$), filtered through Celite® and the solvents removed *in vacuo* to give crude 1,2-diamine. To a solution of the crude 1,2-diamine in CH_2Cl_2 (10.0 mL) at -78 °C was added DIPEA (1.50 mmol) quickly followed by the dropwise addition of TFAA (1.50 mmol). The reaction was stirred at -78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction was quenched by the addition of 2 M HCl (10 mL), the layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to give crude *β*-aminoacetamide, which was purified by flash column chromatography.

General Procedure L

To a solution of *β*-nitroamine (1.00 mmol) in EtOH (20.0 mL) and EtOAc (20.0 mL) at rt was added 6 M HCl (20.0 mmol) followed by Zn dust (10.0 mmol) in one portion. The grey suspension was stirred vigorously rt for 1 h before removal of the solvents *in vacuo*. The residue was neutralised by the addition of $NaHCO_{3(s)}$ and the product extracted into EtOAc (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to give crude 1,2-diamine.

To a solution of the crude 1,2-diamine in CH_2Cl_2 (10.0 mL) at -78 °C was added DIPEA (1.50 mmol) quickly followed by the dropwise addition of TFAA (1.50 mmol). The reaction was stirred at -78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction was quenched by the addition of 2 M HCl (10 mL), the layers were separated and the aqueous layer further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to give crude *β*-aminoacetamide, which was purified by flash column chromatography.

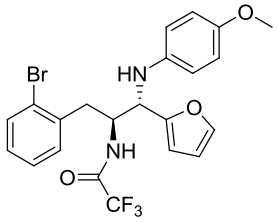
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (236a)



236a

Prepared using general procedure J. *β*-Nitroacetamide **232a** (893 mg, 1.66 mmol) afforded crude *β*-aminoacetamide **236a** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-aminoacetamide **236a** as a white solid (751 mg, 89%); mp 166-169 °C; R_f 0.33 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3303 (N-H), 3065-2834 (C-H), 1702 (C=O), 1512 (C=C), 1180 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.84 (1H, dd, *J* = 14.1, 11.1, C*H*$_2$), 3.15 (1H, dd, *J* = 14.1, 3.7, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.33 (1H, br s, N*H*PMP), 4.70 (1H, d, *J* = 3.7, C*H*Ph), 4.75 (1H, m, C*H*CH$_2$), 6.39 (1H, br d, *J* = 9.4, N*H*TFA), 6.56 (2H, dm, *J* = 8.9, Ar*H*), 6.72 (2H, dm, *J* = 8.9, Ar*H*), 7.10 (2H, m, Ar*H*), 7.22 (1H, td, *J* = 7.5, 0.9, Ar*H*), 7.35 (1H, m, Ar*H*), 7.40- 7.43 (4H, m, Ar*H*), 7.52 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.7 (*C*H$_2$), 55.4 (*C*HCH$_2$), 55.8 (O*C*H$_3$), 62.2 (*C*HPh), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.7 (1C, q, *J* = 288.0, *C*F$_3$), 124.9 (Ar*C*CH$_2$), 127.3 (Ar*C*H), 127.9 (Ar*C*H), 128.3 (Ar*C*H), 129.0 (Ar*C*H), 129.1 (Ar*C*H), 131.0 (Ar*C*H), 133.1 (Ar*C*H), 136.1 (Ar*C*Br), 138.3 (Ar*C*CHN), 140.6 (Ar*C*N), 152.8 (Ar*C*O), 157.4 (1C, q, *J* = 37.2, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$); m/z (ESI^+) 507+509 (26%, M^++H), 429 (100%, M^+-Br); HRMS $C_{24}H_{23}(^{79}Br)F_3N_2O_2$ calcd. 507.0890, found 507.0879; Anal. calcd. for $C_{24}H_{22}BrF_3N_2O_2$: C, 56.82; H, 4.37; N, 5.52; found: C, 56.63; H, 4.31; N, 5.29%.

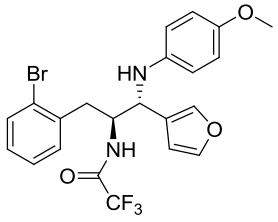
_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-1-(furan-2-yl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236b)



236b

Prepared using general procedure J. *β*-Nitroacetamide **232b** (586 mg, 1.11 mmol) afforded crude *β*-aminoacetamide **236b** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) and subsequent recrystallisation from toluene/Pet. ether yielded pure *β*-aminoacetamide **236b** as a white solid (501 mg, 91%); mp 131-133 °C; R_f 0.24 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3306 (N-H), 3113-2834 (C-H), 1703 (C=O), 1511 (C=C), 1244 (C-O), 1232, 1207, 1167 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.94 (1H, dd, *J* = 14.0, 10.2, C*H*$_2$), 3.13 (1H, dd, *J* = 14.0, 4.8, C*H*$_2$), 3.74 (3H, s, O*CH*$_3$), 3.98 (1H, br s, N*H*), 4.71 (1H, d, *J* = 4.0, C*H*NPMP), 4.80 (1H, ddd, *J* = 14.4, 9.7, 4.6, C*H*NHTFA), 6.32 (1H, d, *J* = 3.3, Furyl-3-*H*), 6.37 (1H, dd, *J* = 3.3, 1.9, Furyl-4-*H*), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.67 (1H, br d, *J* = 9.4, N*H*TFA), 6.76 (2H, dm, *J* = 8.9, Ar*H*), 7.12 (1H, td, *J* = 7.6, 1.6, Ar*H*), 7.21 (1H, dd, *J* = 7.7, 1.7, Ar*H*), 7.25 (1H, td, *J* = 7.5, 1.2, Ar*H*), 7.45 (1H, app dd, *J* = 1.7, 0.7, Furyl-5-*H*), 7.55 (1H, dd, *J* = 8.0, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.0 (*C*H_2), 54.0 (*C*HNHTFA), 55.8 (O*C*H_3), 56.5 (*C*HFuryl), 108.8 (Furyl-3-*C*H), 110.8 (Furyl-4-*C*H), 114.9 (Ar*C*H), 115.8 (1C, q, *J* = 288.3, *C*F_3), 116.1 (Ar*C*H), 125.0 (Ar*C*), 127.8 (Ar*C*H), 129.0 (Ar*C*H), 131.3 (Ar*C*H), 133.2 (Ar*C*H), 136.2 (Ar*C*), 140.3 (Ar*C*N), 142.8 (Furyl-5-*C*H), 152.0 (Furyl-2-*C*), 153.4 (Ar*C*O), 157.2 (1C, q, *J* = 37.0, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 496+498 (4%, M^+), 202 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{22}H_{20}(^{79}Br)F_3N_2O_3$ calcd. 496.0604, found 496.0614; Anal. calcd. for $C_{22}H_{20}BrF_3N_2O_3$: C, 53.13; H, 4.05; N, 5.63; found: C, 53.44; H, 4.16; N, 5.89%.

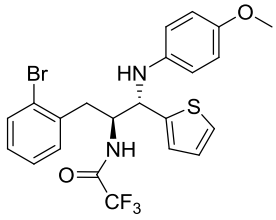
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(furan-3-yl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236c)



236c

Prepared using general procedure J. *β*-Nitroacetamide **232c** (511 mg, 0.969 mmol) afforded crude *β*-aminoacetamide **236c** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) and subsequent recrystallisation from toluene/Pet. ether yielded pure *β*-nitroacetamide **236c** as a white solid (448 mg, 93%); mp 131-133 °C; R_f 0.46 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3398 (N-H), 3312 (N-H), 3111-2835 (C-H), 1705 (C=O), 1511 (C=C), 1244 (C-O), 1230, 1209 (C-F), 1164 (C-F), 1027 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.91 (1H, dd, *J* = 13.9, 10.9, C*H*$_2$), 3.17 (1H, dd, *J* = 14.0, 4.0, C*H*$_2$), 3.74 (1H, s, OC*H*$_3$), 3.90 (1H, br s, N*H*), 4.65 (1H, d, *J* = 3.2, C*H*NPMP), 4.72 (1H, m, C*H*NTFA), 6.45 (1H, s, Furyl-4-*H*), 6.52 (1H, d, *J* = 9.3, N*H*), 6.63 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 8.9, Ar*H*), 7.12 (1H, td, *J* = 7.7, 1.5, Ar*H*), 7.17 (1H, dd, *J* = 7.6, 1.4, Ar*H*), 7.25 (1H, t, *J* = 7.4, Ar*H*), 7.45-7.47 (2H, m, Furyl-2-*H* + Furyl-5-*H*), 7.55 (1H, d, *J* = 8.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.6 (*C*H$_2$), 54.5 (*C*HNPMP), 55.4 (*C*HNTFA), 55.8 (O*C*H$_3$), 109.3 (Furyl-4-*C*H), 115.0 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F$_3$), 115.8 (Ar*C*H), 123.8 (Furyl-3-*C*), 124.9 (Ar*C*CH$_2$), 127.9 (Ar*C*H), 129.1 (Ar*C*H), 131.2 (Ar*C*H), 133.2 (Ar*C*H), 136.1 (Ar*C*Br), 140.5 (Furyl-2-*C*H), 140.6 (Ar*C*N), 144.2 (Furyl-5-*C*H), 153.2 (Ar*C*O), 157.3 (1C, q, *J* = 37.2, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 496+498 (1:1, 2%, M^+), 202 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{22}H_{20}(^{79}Br)F_3N_2O_3$ calcd. 496.0604, found 496.0598; Anal. calcd. for $C_{22}H_{20}BrF_3N_2O_3$: C, 53.13; H, 4.05; N, 5.63; found: C, 53.27; H, 4.02; N, 5.52%.

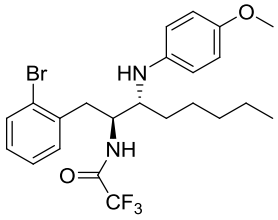
_N_-((1_S_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-(thiophen-2-yl)propan-2-yl)-2,2,2-trifluoroacetamide (236d)



236d

Prepared using general procedure J. *β*-Nitroacetamide **232d** (516 mg, 0.950 mmol) afforded crude *β*-aminoacetamide **236d** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) and subsequent recrystallisation from toluene/Pet. ether yielded pure *β*-nitroacetamide **236d** as a white solid (402 mg, 82%); mp 131-133 °C; R_f 0.46 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3298 (N-H), 3104-2834 (C-H), 1700 (C=O), 1512 (C=C), 1244 (C-O), 1233 (C-F), 1207 (C-F), 1178 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.93 (1H, dd, *J* = 14.0, 10.8, C*H*$_2$), 3.20 (1H, dd, *J* = 14.1, 4.1, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.23 (1H, d, *J* = 6.7, N*H*PMP), 4.79 (1H, m, C*H*NTFA), 4.93 (1H, dd, *J* = 6.6, 3.5, C*H*NPMP), 6.49 (1H, br d, *J* = 9.4, N*H*TFA), 6.61 (2H, dm, *J* = 8.9, Ar*H*), 6.75 (2H, dm, *J* = 8.9, Ar*H*), 7.07 (1H, dd, *J* = 5.0, 3.5, thiophenyl-5-*H*), 7.11-7.14 (2H, m, Ar*H* + thiophenyl-4-*H*), 7.18 (1H, dd, *J* = 7.7, 1.7, Ar*H*), 7.26 (1H, td, *J* = 7.5, 1.4, Ar*H*), 7.31 (1H, dd, *J* = 5.1, 1.1, thiophenyl-3-*H*), 7.55 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.0 (*C*H_2), 55.2 (*C*HNTFA), 55.8 (O*C*H_3), 59.0 (*C*HNPMP), 114.9 (Ar*C*H), 115.7 (Ar*C*H), 115.7 (1C, q, *J* = 288.3, *C*F_3), 125.0 (Ar*C*CH_2), 125.5 (thiophenyl-3-*C*H), 125.6 (thiophenyl-4-*C*H), 127.5 (thiophenyl-5-*C*H), 127.9 (Ar*C*H), 129.1 (Ar*C*H), 131.1 (Ar*C*H), 133.2 (Ar*C*H), 136.0 (Ar*C*Br), 140.4 (Ar*C*N), 143.0 (thiophenyl-2-*C*), 153.2 (Ar*C*O), 157.6 (1C, q, *J* = 37.3, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 514 + 512 (3%, M^+), 218 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{22}H_{20}(^{79}Br)F_3N_2O_2S$ calcd. 512.0376, found 512.0374; Anal. calcd. for $C_{22}H_{20}BrF_3N_2O_2S$: C, 51.47; H, 3.93; N, 5.46; found: C, 51.62; H, 3.86; N, 5.41%.

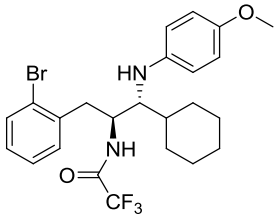
_N_-((2_S_*,3_R_*)-1-(2-Bromophenyl)-3-((4-methoxyphenyl)amino)octan-2-yl)-2,2,2-trifluoroacetamide (236e)



236e

Prepared using general procedure J. *β*-Nitroacetamide **232e** (999 mg, 1.88 mmol) afforded crude *β*-aminoacetamide **236e** as a pale brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236e** as an off-white solid (899 mg, 95%); mp 51-53 °C; R_f 0.23 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3391 (N-H), 3297 (N-H), 3105-2834 (C-H), 1702 (C=O), 1510 (C=C), 1232 (C-O), 1208 (C-F), 1178 (C-F), 1163 (C-F), 1039 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.9, CH_2CH_3), 1.24-1.32 (4H, m, $(CH_2)_2$)CH_3), 1.37-1.47 (2H, m, $CHCH_2CH_2$), 1.55-1.61 (1H, m, $CHCH_2$), 1.65-1.71 (1H, m, $CHCH_2$), 2.84 (1H, dd, *J* = 13,7, 11.3, $ArCH_2$), 3.13 (1H, br s, NHPMP), 3.20 (1H, dd, *J* = 13.7, 3.9, $ArCH_2$), 3.55 (1H, m, CHNHPMP), 3.77 (3H, s, OCH_3), 4.49 (1H, m, CHNHTFA), 6.61-6.65 (3H, m, NHTFA + 2 x ArH), 6.79 (2H, dm, *J* = 8.9, ArH), 7.12 (1H, td, *J* = 7.7, 1.5, ArH), 7.19 (1H, dd, *J* = 7.6, 1.5, ArH), 7.25 (1H, td, *J* = 7.4, 0.8, ArH), 7.55 (1H, dd, *J* = 8.0, 0.7, ArH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 22.6 (CH_2), 26.3 (CH_2), 31.8 (CH_2), 33.5 (CH_2), 35.1 (CH_2Ar), 53.6 (CHNHTFA), 55.8 (OCH_3), 59.0 (CHNHPMP), 115.2 (ArCH), 115.6 (ArCH), 115.8 (1C, q, *J* = 288.2, CF_3), 125.0 ($ArCCH_2$), 127.7 (ArCH), 128.9 (ArCH), 131.3 (ArCH), 133.1 (ArCH), 136.5 (ArCBr), 142.0 (ArCN), 153.0 (ArCO), 156.6 (1C, q, *J* = 36.9, CCF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, CF_3); m/z (EI) 500+502 (4%, M^+), 206 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{23}H_{28}(^{79}Br)F_3N_2O_2$ calcd. 500.1281, found 500.1289; Anal. calcd. for $C_{23}H_{28}BrF_3N_2O_2$: C, 55.10; H, 5.63; N, 5.59; found: C, 55.33; H, 5.65; N, 5.61%.

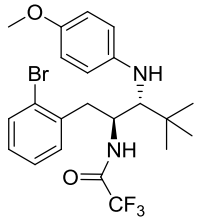
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-cyclohexyl-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236f)



236f

Prepared using general procedure K. *β*-Aminohydroxylamine **278** (146 mg, 0.337 mmol) afforded crude *β*-aminoacetamide **236f** as a yellow oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236f** as a white solid (141 mg, 81%); mp 60-63 °C; R_f 0.52 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3360 (N-H), 3305 (N-H), 3105-2853 (C-H), 1703 (C=O), 1509 (C=C), 1243, 1232, 1207 (C-F), 1162 (C-F), 1039, 1027 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (1H, qd, *J* = 12.6, 2.9, Cy*H*), 1.11-1.30 (4H, m, Cy*H*), 1.50-1.56 (1H, m, Cy*H*CHN), 1.67 (1H, d, *J* = 10.9, Cy*H*), 1.71 (1H, d, *J* = 11.5, Cy*H*), 1.80-1.82 (1H, m, Cy*H*), 1.91 (1H, d, *J* = 13.2, Cy*H*), 2.04 (1H, d, *J* = 12.4, Cy*H*), 2.87 (1H, dd, *J* = 13.7, 11.6, ArC*H*$_2$), 3.14 (1H, dd, *J* = 13.8, 3.7, ArC*H*$_2$), 3.24 (1H, d, *J* = 9.2, N*H*PMP), 3.32 (1H, td, *J* = 9.0, 3.5, C*H*NPMP), 3.76 (3H, s, OC*H*$_3$), 4.66 (1H, m, C*H*NTFA), 6.62 (2H, dm, *J* = 8.9, Ar*H*), 6.67 (1H, d, *J* = 9.5, N*H*TFA), 6.78 (2H, dm, *J* = 8.9, Ar*H*), 7.10 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.19 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.24 (1H, td, *J* = 7.5, 1.0, Ar*H*), 7.54 (1H, dd, *J* = 8.1, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.0 (Cy*C*H$_2$), 26.0 (Cy*C*H$_2$), 26.2 (Cy*C*H$_2$), 30.5 (Cy*C*H$_2$),30.5 (Cy*C*H$_2$), 34.6 (*C*H$_2$CHNTFA), 42.2 (Cy*C*HCHN), 51.8 (*C*HNTFA), 55.8 (O*C*H$_3$), 63.9 (*C*HNPMP), 114.6 (Ar*C*H), 115.2 (Ar*C*H), 115.8 (1C, q, *J* = 288.2, *C*F$_3$), 125.1 (Ar*C*CH$_2$), 127.7 (Ar*C*H), 128.8 (Ar*C*H), 131.4 (Ar*C*H), 133.0 (Ar*C*H), 136.5 (Ar*C*Br), 143.3 (Ar*C*N), 152.7 (Ar*C*O), 156.4 (1C, q, *J* = 36.8, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$); m/z (EI) 512+514 (1:1, 5%, M^+), 218 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{24}H_{28}(^{79}Br)F_3N_2O_2$ calcd. 512.1281, found 512.1276; Anal. calcd. for $C_{24}H_{28}BrF_3N_2O_2$: C, 56.15; H, 5.50; N, 5.46; found: C, 55.92; H, 5.48; N, 5.42%.

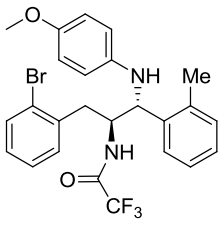
_N_-((2_S_*,3_R_*)-1-(2-Bromophenyl)-3-((4-methoxyphenyl)amino)-4,4-dimethylpentan-2-yl)-2,2,2-trifluoroacetamide (236g)



236g

Prepared using general procedure L. Crude *β*-nitroamine **230g** (4.52 mmol) afforded crude *β*-aminoacetamide **236g** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236g** as a white solid (1.42 g, 65%, *anti*:*syn* = 6.7:1); mp 82-84 °C; R_f 0.51 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3399 (N-H), 3311 (N-H), 3062-2833 (C-H), 1706 (C=O), 1509 (C=C), 1243 (C-O), 1231 (C-F), 1207 (C-F), 1159 (C-F), 1038 (C-O), 1023 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (9H, s, C(CH_3)$_3$), 2.91 (1H, dd, *J* = 13.6, 12.1, CH_2), 3.23 (1H, dd, *J* = 13.7, 3.6, CH_2), 3.45 (1H, br s, C*H*C(CH_3)$_3$), 3.54 (1H, br s, N*H*PMP), 3.76 (3H, s, OCH_3), 4.74 (1H, m, C*H*CH_2), 6.55 (1H, br d, *J* = 9.2, N*H*TFA), 6.66 (2H, dm, *J* = 9.0, Ar*H*), 6.79 (2H, dm, *J* = 9.0, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.7, Ar*H*), 7.14 (1H, dd, *J* = 7.7, 1.7, Ar*H*), 7.23 (1H, td, *J* = 7.5, 1.2, Ar*H*), 7.53 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.1 (C(*C*H_3)$_3$), 36.2 (*C*H_2), 36.4 (*C*(CH_3)$_3$), 52.3 (*C*HNHTFA), 55.9 (O*C*H_3), 67.0 (*C*HNHPMP), 114.7 (Ar*C*H), 115.3 (Ar*C*H), 115.7 (1C, q, *J* = 288.4, *C*F_3), 125.0 (Ar*C*CH_2), 127.7 (Ar*C*H), 128.8 (Ar*C*H), 131.4 (Ar*C*H), 133.0 (Ar*C*H), 136.5 (Ar*C*Br), 143.3 (Ar*C*N), 152.6 (Ar*C*O), 156.0 (1C, q, *J* = 36.9, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.5 (3F, s, C*F*$_3$); m/z (EI) 486+488 (1:1, 13%, M^+), 429+431 (1:1, 22%, M^+-C(CH_3)$_3$), 192 (100%, PMPNHC$^+$C(CH_3)$_3$); HRMS $C_{22}H_{26}(^{79}Br)F_3N_2O_2$ calcd. 486.1124, found 486.1134; Anal. calcd. for $C_{22}H_{26}BrF_3N_2O_2$: C, 54.22; H, 5.38; N, 5.75; found: C, 54.11; H, 5.32; N, 5.72%.

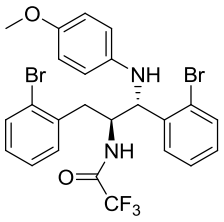
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-(o-tolyl)propan-2-yl)-2,2,2-trifluoroacetamide (236h)



236h

Prepared using general procedure J. *β*-Nitroacetamide **232h** (159 mg, 0.288 mmol) afforded crude *β*-aminoacetamide **236h** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236h** as a white solid (138 mg, 91%); mp 190-192 °C; R_f 0.51 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3409 (N-H), 3327 (N-H), 3063-2834 (C-H), 1703 (C=O), 1511 (C=C), 1243, 1232, 1211 (C-F), 1169 (C-F), 1034 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.55 (3H, s, ArC*H*$_3$), 2.88 (1H, dd, *J* = 13.7, 11.9, C*H*$_2$), 3.14 (1H, dd, *J* = 13.8, 3.0, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.24 (1H, br s, N*H*PMP), 4.65 (1H, m, C*H*NTFA), 4.96 (1H, d, *J* = 3.8, C*H*PMP), 6.58 (2H, dm, *J* = 8.9, Ar*H*), 6.70 (1H, br d, *J* = 9.2, N*H*TFA), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 7.06 (1H, dd, *J* = 7.6, 1.0, Ar*H*), 7.08 (1H, dd, *J* = 7.7, 1.4, Ar*H*), 7.19-7.26 (4H, m, Ar*H*), 7.31-7.33 (1H, m, Ar*H*), 7.50 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.6 (*C*H$_3$Ar), 35.1 (*C*H$_2$), 54.2 (*C*HNTFA), 55.8 (O*C*H$_3$), 58.5 (*C*HNPMP), 115.0 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F$_3$), 115.9 (Ar*C*H), 124.8 (Ar*C*CH$_2$), 125.9 (Ar*C*H), 126.5 (Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 129.0 (Ar*C*H), 131.0 (Ar*C*H), 131.5 (Ar*C*H), 133.1 (Ar*C*H), 136.2 (Ar*C*CHN), 136.3 (Ar*C*Br), 136.4 (Ar*C*CH$_3$), 140.5 (Ar*C*N), 153.1 (Ar*C*O), 157.1 (1C, q, *J* = 37.1, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 520+522 (10%, M^+), 226 (100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{25}H_{24}(^{79}Br)F_3N_2O_2$ calcd. 520.0968, found 520.0974; Anal. calcd. for $C_{25}H_{24}BrF_3N_2O_2$: C, 57.59; H, 4.64; N, 5.37; found: C, 57.88; H, 4.63; N, 5.29%.

_N_-((1_R_*,2_S_*)-1,3-Bis(2-bromophenyl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236i)

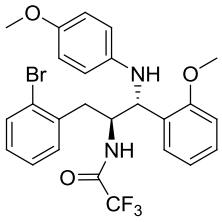


236i

Prepared using general procedure L. Crude *β*-nitroamine **230i** (4.15 mmol) afforded crude *β*-aminoacetamide **236i** as a brown oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236i** as a white solid (1.50 g, 62%, *anti*:*syn* = 14:1); mp 176-178 °C; R_f 0.27 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3409 (N-H), 3268 (N-H), 3106-2832 (C-H), 1702 (C=O), 1510 (C=C), 1240 (C-O), 1232, 1208 (C-F), 1182 (C-F), 1157 (C-F), 1033, 1017 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.30 (1H, dd, *J*

= 14.1, 11.0, CH_2), 3.43 (1H, dd, *J* = 14.2, 3.5, CH_2), 3.71 (3H, s, OCH_3), 4.47 (1H, br s, N*H*PMP), 4.69 (1H, m, C*H*CH_2), 5.09 (1H, br s, C*H*NPMP), 6.54 (2H, br d, *J* = 7.5, Ar*H*), 6.56 (1H, br d, *J* = 10.3, N*H*TFA), 6.73 (2H, d, *J* = 8.8, Ar*H*), 7.11 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.16 (1H, td, *J* = 7.7, 1.4, Ar*H*), 7.17 (1H, dd, *J* = 7.6, 1.5, Ar*H*), 7.23 (1H, td, *J* = 7.4, 0.9, Ar*H*), 7.29 (1H, td, *J* = 7.6, 0.7, Ar*H*), 7.40 (1H, dd, *J* = 7.8, 1.4, Ar*H*), 7.53 (1H, dd, *J* = 8.0, 0.8, Ar*H*), 7.59 (1H, dd, *J* = 8.0, 0.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.2 (*C*H_2), 54.8 (*C*HCH_2), 55.8 (OCH_3), 60.9 (*C*HNPMP), 115.0 (Ar*C*H), 115.3 (Ar*C*H), 115.6 (1C, q, *J* = 287.9, *C*F_3), 124.6 (Ar*C*CH_2), 124.9 (Ar*C*CHN), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 129.1 (Ar*C*H), 129.8 (Ar*C*H), 131.2 (Ar*C*H), 133.2 (Ar*C*H), 133.3 (Ar*C*H), 136.1 (Ar*C*Br), 137.8 (Ar*C*Br), 139.9 (Ar*C*N), 152.9 (Ar*C*O), 156.9 (1C, q, *J* = 37.2, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.5 (3F, s, C*F*$_3$); m/z (EI) 584+586+588 (1:2:1, 97%, M^+), 290+292 (1:1, 100%, M^+-$C_{10}H_8BrF_3NO$); HRMS $C_{24}H_{21}(^{79}Br)_2F_3N_2O_2$ calcd. 583.9916, found 583.9924; Anal. calcd. for $C_{24}H_{21}Br_2F_3N_2O_2$: C, 49.17; H, 3.61; N, 4.78; found: C, 49.43; H, 3.34; N, 4.97%.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(2-methoxyphenyl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236j)

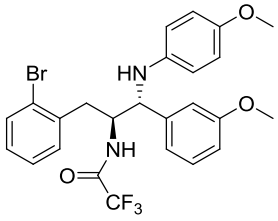


236j

Prepared using general procedure J. *β*-Nitroacetamide **232j** (154 mg, 0.271 mmol) afforded crude *β*-aminoacetamide **236j** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236j** as a white solid (136 mg, 94%); mp 137-138 °C; R_f 0.41 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3373 (N-H), 3062-2836 (C-H), 1710 (C=O), 1511 (C=C), 1235 (C-O), 1208 (C-F), 1163 (C-F), 1027 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.87 (1H, dd, *J* = 14.2, 10.7, CH_2), 3.36 (1H, dd, *J* = 14.2, 3.7, CH_2), 3.71 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.39 (1H, br s, N*H*PMP), 4.71 (1H, qdd, *J* = 10.0, 6.2, 3.8, C*H*NTFA), 4.96 (1H, d, *J* = 6.1, C*H*NPMP), 6.57 (2H, dm, *J* = 8.9, Ar*H*), 6.70 (1H, d, *J* = 9.3, N*H*TFA), 6.72 (2H, dm, *J* = 8.9, Ar*H*), 6.92-6.94 (2H, m, Ar*H*), 7.09 (1H, td, *J* = 7.6, 1.6, Ar*H*), 7.16 (1H, dd, *J* = 7.7, 1.7, Ar*H*), 7.22 (1H, td, *J* = 7.4, 1.2, Ar*H*), 7.24-7.28 (2H, m, Ar*H*), 7.52 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151

MHz, $CDCl_3$) δ 37.6 (*C*H_2), 54.5 (*C*HNTFA), 55.6 (O*C*H_3), 55.8 (O*C*H_3), 57.5 (*C*HNPMP), 110.8 (Ar*C*H), 114.9 (Ar*C*H), 115.4 (Ar*C*H), 115.8 (1C, q, *J* = 288.3, *C*F_3), 121.3 (Ar*C*H), 125.0 (Ar*C*CH_2), 126.5 (Ar*C*CHN), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.7 (Ar*C*H), 129.2 (Ar*C*H), 131.2 (Ar*C*H), 133.0 (Ar*C*H), 136.8 (Ar*C*Br), 140.7 (Ar*C*N), 152.7 (Ar*C*O), 156.8 (1C, q, *J* = 36.8, *C*CF_3), 157.1 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.6 (3F, s, C*F*$_3$); m/z (CI) 537+539 (1:1, 12%, M^++H), 414+416 (1:1, 15%, M^+-NHPMP), 301+303 (5%, M^+- $C_9H_9F_3N_2O_2$), 242 (25%, M^+- $C_{10}H_8BrF_3NO$); HRMS $C_{25}H_{25}(^{79}Br)F_3N_2O_3$ calcd. 537.1001, found 537.1013; Anal. calcd. for $C_{25}H_{24}BrF_3N_2O_3$: C, 55.88; H, 4.50; N, 5.21; found: C, 55.58; H, 4.40; N, 5.25%.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(3-methoxyphenyl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236k)

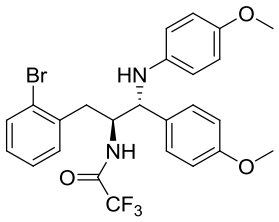


236k

Prepared using general procedure J. *β*-Nitroacetamide **232k** (177 mg, 0.312 mmol) afforded crude *β*-aminoacetamide **236k** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) followed by recrystallisation from toluene/Pet. ether yielded pure *β*-nitroacetamide **236k** as a white solid (137 mg, 82%); mp 130-131 °C; R_f 0.31 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3389 (N-H), 3306 (N-H), 3107-2836 (C-H), 1701 (C=O), 1511 (C=C), 1242, 1232, 1208 (C-F), 1158 (C-F), 1037 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.84 (1H, dd, *J* = 13.9, 11.3, C*H*$_2$), 3.15 (1H, dd, *J* = 14.1, 3.6, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.29 (1H, br s, N*H*PMP), 4.66 (1H, br s, C*H*NPMP), 4.75 (1H, m, C*H*NTFA), 6.42 (1H, d, *J* = 9.4, N*H*TFA), 6.56 (2H, d, *J* = 6.2, Ar*H*), 6.72 (2H, d, *J* = 8.9, Ar*H*), 6.87 (1H, dd, *J* = 8.2, 2.1, Ar*H*), 6.95 (1H, s, Ar*H*), 7.00 (1H, d, *J* = 7.6, Ar*H*), 7.09-7.12 (2H, m, Ar*H*), 7.22 (1H, td, *J* = 7.4, 0.7, Ar*H*), 7.33 (1H, t, *J* = 7.9, Ar*H*), 7.53 (1H, d, *J* = 8.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.8 (*C*H_2), 55.2 (*C*HNTFA), 55.4 (O*C*H_3), 55.8 (O*C*H_3), 62.3 (*C*HNPMP), 112.9 (Ar*C*H), 113.6 (Ar*C*H), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.7 (1C, q, *J* = 288.1, *C*F_3), 119.6 (Ar*C*H), 124.9 (Ar*C*CH_2), 127.9 (Ar*C*H), 129.0 (Ar*C*H), 130.2 (Ar*C*H), 131.0 (Ar*C*H), 133.1 (Ar*C*H), 136.1 (Ar*C*Br), 140.0 (Ar*C*CHN), 140.6 (Ar*C*N), 152.8 (Ar*C*O), 157.4 (1C, q, *J* = 37.3, *C*CF_3), 160.2 (Ar*C*O);

^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (ES$^-$) 536+538 (1:1, 25%, M$^-$), 535+537 (1:1, 100%, M-H$^+$), 457 (18%, M$^-$-Br); HRMS $C_{25}H_{23}(^{79}Br)F_3N_2O_3$ calcd. 535.0844, found 535.0837; Anal. calcd. for $C_{25}H_{24}BrF_3N_2O_3$: C, 55.88; H, 4.50; N, 5.21; found: C, 55.60; H, 4.40; N, 5.16%.

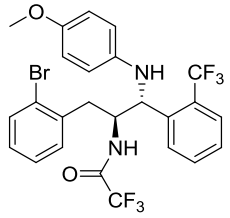
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-(4-methoxyphenyl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236l)



236l

Prepared using general procedure J. *β*-Nitroacetamide **232l** (169 mg, 0.298 mmol) afforded crude *β*-aminoacetamide **236l** as a pale brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236l** as a white solid (146 mg, 91%); mp 173-175 °C; R_f 0.35 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3399 (N-H), 3302 (N-H), 3107-2836 (C-H), 1702 (C=O), 1510 (C=C), 1243 (C-O), 1209 (C-F), 1175 (C-F), 1033 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.81 (1H, dd, *J* = 14.0, 11.2, C*H*$_2$), 3.15 (1H, dd, *J* = 14.1, 3.8, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 4.28 (1H, br s, N*H*PMP), 4.64 (1H, br s, C*H*NPMP), 4.73 (1H, m, C*H*NTFA), 6.33 (1H, d, *J* = 9.4, N*H*TFA), 6.54 (2H, d, *J* = 8.6, Ar*H*), 6.71 (2H, d, *J* = 8.9, Ar*H*), 6.94 (2H, dm, *J* = 8.7, Ar*H*), 7.09-7.10 (1H, m, Ar*H*), 7.11 (1H, d, *J* = 7.4, Ar*H*), 7.22 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.32 (2H, dm, *J* = 8.6, Ar*H*), 7.53 (1H, dd, *J* = 8.3, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.9 (*C*H$_2$), 55.4 (O*C*H$_3$ + *C*HNTFA), 55.8 (O*C*H$_3$), 61.7 (*C*HNPMP), 114.5 (Ar*C*H), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F$_3$), 124.9 (Ar*C*CH$_2$), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 129.0 (Ar*C*H), 130.0 (Ar*C*CHN), 131.0 (Ar*C*H), 133.1 (Ar*C*H), 136.1 (Ar*C*Br), 140.6 (Ar*C*N), 152.7 (Ar*C*O), 157.5 (1C, q, *J* = 37.2, *C*CF$_3$), 159.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (CI) 537+539 (1:1, 100%, M$^+$+H), 536+538 (1:1, 23%, M$^+$), 242 (44%, M$^+$-$C_{10}H_8BrF_3NO$); HRMS $C_{25}H_{25}(^{79}Br)F_3N_2O_3$ calcd. 537.1001, found 537.1008; Anal. calcd. for $C_{25}H_{24}BrF_3N_2O_3$: C, 55.88; H, 4.50; N, 5.21; found: C, 56.03; H, 4.48; N, 5.16%.

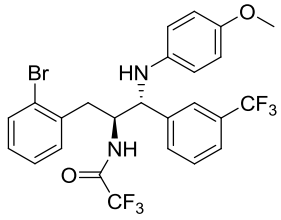
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-(2-(trifluoromethyl)phenyl)propan-2-yl)-2,2,2-trifluoroacetamide (236m)



236m

Prepared using general procedure J. *β*-Nitroacetamide **232m** (824 mg, 1.36 mmol) afforded crude *β*-aminoacetamide **236m** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) and subsequent recrystallisation from toluene/Pet. ether yielded pure *β*-nitroacetamide **236m** as a white solid (642 mg, 82%); mp 140-142 °C; R_f 0.38 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3362 (N-H), 3066-2836 (C-H), 1712 (C=O), 1512 (C=C), 1310, 1243, 1234, 1212, 1161 (C-F), 1118 (C-F), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.06 (1H, dd, *J* = 14.1, 10.1, C*H*$_2$), 3.55 (1H, dd, *J* = 14.1, 3.4, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.30 (1H, br s, N*H*PMP), 4.55 (1H, m, C*H*NTFA), 4.98 (1H, d, *J* = 6.6, C*H*NPMP), 6.40 (1H, d, *J* = 8.8, N*H*TFA), 6.63 (2H, d, *J* = 8.8, Ar*H*), 6.74 (2H, d, *J* = 8.8, Ar*H*), 7.11 (1H, td, *J* = 7.6, 1.4, Ar*H*), 7.19 (1H, dd, *J* = 7.5, 1.4, Ar*H*), 7.24 (1H, t, *J* = 7.4, Ar*H*), 7.38 (1H, t, *J* = 7.7, Ar*H*), 7.52-7.55 (2H, m, Ar*H*), 7.68 (2H, d, *J* = 8.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.7 (*C*H$_2$), 55.5 (*C*HNTFA), 55.7 (O*C*H$_3$), 58.7 (*C*HNPMP), 114.9 (Ar*C*H), 115.5 (1C, q, *J* = 288.2, CO*C*F$_3$), 115.9 (Ar*C*H), 124.7 (1C, q, *J* = 273.9, *C*F$_3$Ar), 124.8 (Ar*C*CH$_2$), 126.2 (1C, q, *J* = 5.9, Ar*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (1C, q, *J* = 29.4, Ar*C*CF$_3$), 128.3 (Ar*C*H), 129.1 (Ar*C*H), 131.3 (Ar*C*H), 132.8 (Ar*C*H), 133.2 (Ar*C*H), 136.1 (Ar*C*Br), 138.9 (Ar*C*CHN), 139.8 (Ar*C*N), 153.2 (Ar*C*O), 156.4 (1C, q, *J* = 37.2, *C*OCF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.8 (3F, s, C*F*$_3$), -57.2 (3F, s, C*F*$_3$); m/z (EI) 574+576 (1:1, 3%, M^+), 280 (100%, M^+-$C_8H_{10}BrF_3NO$); HRMS $C_{25}H_{21}(^{79}Br)F_6N_2O_2$ calcd. 574.0685, found 574.0696; Anal. calcd. for $C_{25}H_{21}BrF_6N_2O_2$: C, 52.19; H, 3.68; N, 4.87; found: C, 51.92; H, 3.45; N, 4.94%.

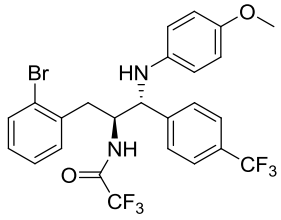
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-(3-(trifluoromethyl)phenyl)propan-2-yl)-2,2,2-trifluoroacetamide (236n)



236n

Prepared using general procedure J. *β*-Nitroacetamide **232n** (688 mg, 1.14 mmol) afforded crude *β*-aminoacetamide **236n** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236n** as a white solid (579 mg, 89%); mp 133-134 °C; R_f 0.24 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3408 (N-H), 3292 (N-H), 3108-2836 (C-H), 1699 (C=O), 1511 (C=C), 1327, 1242, 1233, 1210, 1162 (C-F), 1124 (C-F), 1072, 1033 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.88 (1H, dd, *J* = 14.0, 11.0, C*H*$_2$), 3.16 (1H, dd, *J* = 14.1, 3,8, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 4.40 (1H, br s, N*H*PMP), 4.72 (1H, m, C*H*CH$_2$), 4.77 (1H, d, *J* = 3.8, C*H*NPMP), 6.41 (1H, d, *J* = 9.1, N*H*TFA), 6.55 (2H, dm, *J* = 8.9, Ar*H*), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 7.10-7.12 (2H, m, Ar*H*), 7.23 (1H, t, *J* = 7.5, Ar*H*), 7.52-7.54 (2H, m, Ar*H*), 7.61 (2H, t, *J* = 8.5, Ar*H*), 7.67 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.3 (*C*H$_2$), 55.5 (*C*HCH$_2$), 55.8 (O*C*H$_3$), 62.1 (*C*HNPMP), 115.0 (Ar*C*H), 115.6 (Ar*C*H), 115.6 (1C, q, *J* = 288.0, *C*F$_3$), 124.0 (1C, q, *J* = 272.5, *C*F$_3$), 124.2 (1C, q, *J* = 3.6, Ar*C*H), 124.8 (Ar*C*CH$_2$), 125.2 (1C, q, *J* = 3.5, Ar*C*H), 128.0 (Ar*C*H), 129.2 (Ar*C*H), 129.6 (Ar*C*H), 130.6 (Ar*C*H), 131.0 (Ar*C*H), 131.4 (1C, q, *J* = 32.4, Ar*C*CF$_3$), 133.2 (Ar*C*H), 135.7 (Ar*C*Br), 139.9 (Ar*C*CHN), 140.0 (Ar*C*N), 153.1 (Ar*C*O), 157.6 (1C, q, *J* = 37.4, *C*OCF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$), -63.0 (3F, s, C*F*$_3$); m/z (CI) 575+577 (5%, M^++H), 280 (100%, M^+-$C_8H_{10}BrF_3NO$); HRMS $C_{25}H_{22}(^{79}Br)F_6N_2O_2$ calcd. 575.0769, found 575.0778; Anal. calcd. for $C_{25}H_{21}BrF_6N_2O_2$: C, 52.19; H, 3.68; N, 4.87; found: C, 52.27; H, 3.57; N, 4.85%.

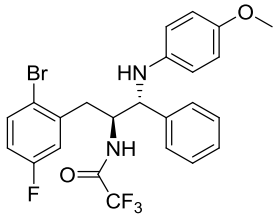
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-(4-(trifluoromethyl)phenyl)propan-2-yl)-2,2,2-trifluoroacetamide (236o)



236o

Prepared using general procedure J. *β*-Nitroacetamide **232o** (176 mg, 0.291 mmol) afforded crude *β*-aminoacetamide **236o** as a pale brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236o** as a white solid (147 mg, 88%); mp 154-156 °C; R_f 0.45 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3402 (N-H), 3293 (N-H), 3106-2836 (C-H), 1701 (C=O), 1512 (C=C), 1326, 1243, 1211, 1166 (C-F), 1125 (C-F), 1068 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.88 (1H, dd, *J* = 14.1, 10.8, C*H*$_2$), 3.15 (1H, dd, *J* = 14.1, 3.8, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.40 (1H, d, *J* = 5.5, N*H*PMP), 4.73-4.78 (2H, m, C*H*NTFA + C*H*NPMP), 6.41 (1H, d, *J* = 8.9, N*H*TFA), 6.53 (2H, dm, *J* = 8.9, Ar*H*), 6.73 (2H, dm, *J* = 8.9, Ar*H*), 7.10-7.13 (2H, m, Ar*H*), 7.23 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.52-7.53 (1H, m, Ar*H*), 7.54 (2H, d, *J* = 8.1, Ar*H*), 7.66 (2H, d, *J* = 8.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.3 (*C*H$_2$), 55.4 (*C*HNTFA), 55.8 (O*C*H$_3$), 62.0 (*C*HNPMP), 115.0 (Ar*C*H), 115.5 (Ar*C*H), 115.6 (1C, q, *J* = 288.2, CO*C*F$_3$), 124.0 (1C, q, *J* = 272.2, *C*F$_3$Ar), 124.8 (Ar*C*CH$_2$), 126.0 (1C, q, *J* = 3.4, Ar*C*H), 127.7 (Ar*C*H), 128.0 (Ar*C*H), 129.2 (Ar*C*H), 130.5 (1C, q, *J* = 32.5, Ar*C*CF$_3$), 131.0 (Ar*C*H), 133.2 (Ar*C*H), 135.6 (Ar*C*Br), 140.0 (Ar*C*N), 142.8 (Ar*C*CHN), 153.1 (Ar*C*O), 157.6 (1C, q, *J* = 37.4, *C*OCF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$), -63.0 (3F, s, C*F*$_3$); m/z (CI) 575+577 (1:1, 100%, M^++H), 574+576 (1:1, 7%, M^+); HRMS $C_{25}H_{22}(^{79}Br)F_6N_2O_2$ calcd. 575.0769, found 575.0771; Anal. calcd. for $C_{25}H_{21}BrF_6N_2O_2$: C, 52.19; H, 3.68; N, 4.87; found: C, 52.06; H, 3.60; N, 4.85%.

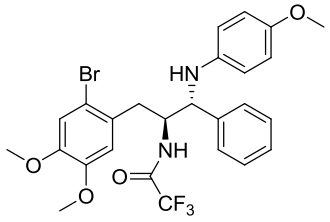
_N_-((1_R_*,2_S_*)-3-(2-Bromo-5-fluorophenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (236p)



236p

Prepared using general procedure J. *β*-Nitroacetamide **232p** (649 mg, 1.17 mmol) afforded crude *β*-aminoacetamide **236p** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236p** as a white solid (546 mg, 89%); mp 148-150 °C; R_f 0.26 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3397 (N-H), 3301 (N-H), 3107-2835 (C-H), 1700 (C=O), 1512 (C=C), 1471, 1236 (C-O), 1210 (C-F), 1179 (C-O), 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.80 (1H, dd, *J* = 14.0, 11.2, C*H*$_2$), 3.13 (1H, dd, *J* = 14.0, 3.5, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 4.27 (1H, br s, N*H*PMP), 4.70 (1H, s, C*H*NPMP), 4.74 (1H, m, C*H*NTFA), 6.47 (1H, d, *J* = 9.4, N*H*TFA), 6.57 (2H, d, *J* = 8.5, Ar*H*), 6.72 (2H, dm, *J* = 8.9, Ar*H*), 6.83-6.86 (2H, m, Ar*H*), 7.33-7.36 (1H, m, Ar*H*), 7.39-7.43 (4H, m, Ar*H*), 7.47 (1H, dd, *J* = 9.6, 5.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.8 (*C*H_2), 55.1 (*C*HNTFA), 55.8 (O*C*H_3), 62.2 (*C*HNPMP), 114.9 (Ar*C*H), 115.7 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F_3), 116.3 (1C, d, *J* = 22.3, Ar*C*H), 118.0 (1C, d, *J* = 22.8, Ar*C*H), 118.9 (1C, d, *J* = 3.2, Ar*C*CH_2), 127.2 (Ar*C*H), 128.4 (Ar*C*H), 129.2 (Ar*C*H), 134.3 (1C, d, *J* = 8.1, Ar*C*H), 138.1 (Ar*C*CHN), 138.3 (1C, d, *J* = 7.4, Ar*C*Br), 140.4 (Ar*C*N), 153.0 (Ar*C*O), 157.4 (1C, q, *J* = 37.3, *C*CF_3), 161.9 (1C, d, *J* = 248.2, Ar*C*F); ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.6 (1F, m, Ar*F*), -76.3 (3F, s, C*F*$_3$); m/z (EI) 524+526 (1:1, 5%, M^+), 446 (3%, M^+-Br), 212 (100%, M^+-$C_{10}H_7BrF_4NO$); HRMS $C_{24}H_{21}(^{79}Br)F_4N_2O_2$ calcd. 524.0717, found 524.0704; Anal. calcd. for $C_{24}H_{21}BrF_4N_2O_2$: C, 54.87; H, 4.03; N, 5.33; found: C, 54.91; H, 3.97; N, 5.28%.

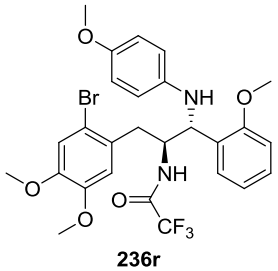
_N_-((1_R_*,2_S_*)-3-(2-Bromo-4,5-dimethoxyphenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (236q)



236q

Prepared using general procedure J. *β*-Nitroacetamide **232q** (89 mg, 0.15 mmol) afforded crude *β*-aminoacetamide **236q** as a pale brown oil. Purification by flash column chromatography (60% Et_2O/Pet. ether) yielded pure *β*-nitroacetamide **236q** as a white solid (67 mg, 79%); mp 167-169 °C; R_f 0.27 (60% Et_2O/Pet. ether); IR υ_{max} (neat) 3410 (N-H), 3296 (N-H), 3113-2837 (C-H), 1695 (C=O), 1509 (C=C), 1259, 1241 (C-O), 1217 (C-F), 1178 (C-F), 1166 (C-F), 1034 (C-O), cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.81 (1H, dd, *J* = 14.3, 10.7, C*H*$_2$), 3.10 (1H, dd, *J* = 14.3, 3.6, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 4.33 (1H, d, *J* = 6.1, N*H*PMP), 4.68 (1H, d, *J* = 5.2, C*H*Ph), 4.70 (1H, m, C*H*CH_2), 6.37 (1H, br d, *J* = 9.0, N*H*TFA), 6.55 (2H, dm, *J* = 8.9, Ar*H*), 6.57 (1H, s, Ar*H*), 6.71 (2H, dm, *J* = 8.9, Ar*H*), 6.96 (1H, s, Ar*H*), 7.33 (1H, m, Ar*H*), 7.40 (4H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.3 (*C*H_2), 55.6 (*C*HNTFA), 55.8 (O*C*H_3), 56.1 (O*C*H_3), 56.2 (O*C*H_3), 62.3 (*C*HNPMP), 113.1 (Ar*C*H), 114.7 (Ar*C*CH_2), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.5 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F_3), 127.3 (Ar*C*H), 127.8 (Ar*C*Br), 128.3 (Ar*C*H), 129.1 (Ar*C*H), 138.4 (Ar*C*CHNH), 140.5 (Ar*C*N), 148.7 (Ar*C*O), 148.8 (Ar*C*O), 152.8 (Ar*C*O), 157.5 (1C, q, *J* = 37.2, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (FAB$^+$) 591+589 (12%, M+Na^+), 212 (100%, $C_{12}H_{12}BrF_3NO_3$); HRMS $C_{26}H_{26}(^{79}Br)F_3N_2O_4Na$ calcd. 589.0926, found 589.0912; Anal. calcd. for $C_{26}H_{26}BrF_3N_2O_4$: C, 55.04; H, 4.62; N, 4.94; found: C, 55.38; H, 4.53; N, 4.75%.

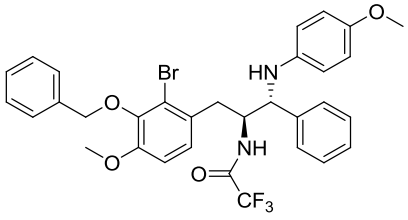
_N_-((1_R_*,2_S_*)-3-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-methoxyphenyl)-1-((4-methoxyphenyl)amino)propan-2-yl)-2,2,2-trifluoroacetamide (236r)



236r

Prepared using general procedure L. Crude *β*-nitroamine **230r** (3.30 mmol) afforded crude *β*-aminoacetamide **236r** as a brown oil. Purification by flash column chromatography (30% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236r** as a white solid (793 mg, 40%, *anti*:*syn* = 9:1); mp 73-75 °C; R_f 0.38 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3365 (N-H), 3069-2840 (C-H), 1714 (C=O), 1508 (C=C), 1463, 1439, 1258, 1234 (C-O), 1214 (C-F), 1161 (C-F), 1028 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.90 (1H, dd, *J* = 14.3, 9.9, C*H*$_2$), 3.31 (1H, dd, *J* = 14.4, 3.0, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.71 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 4.65 (1H, dtd, *J* = 7.9, 7.9, 3.4, C*H*NTFA), 4.92 (1H, d, *J* = 6.5, C*H*NPMP), 6.56 (2H, d, *J* = 8.3, Ar*H*), 6.69 (1H, s, Ar*H*), 6.71 (2H, dm, *J* = 8.9, Ar*H*), 6.83 (1H, br s, N*H*TFA), 6.91-6.93 (2H, m, Ar*H*), 6.98 (1H, s, Ar*H*), 7.25 (2H, t, *J* = 7.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.0 (*C*H$_2$), 54.8 (*C*HNTFA), 55.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 55.9 (O*C*H$_3$), 56.2 (O*C*H$_3$), 57.0 (*C*HNPMP), 110.8 (Ar*C*H), 113.5 (Ar*C*H), 114.8 (Ar*C*CH$_2$), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.5 (Ar*C*H), 115.8 (1C, q, *J* = 288.4, *C*F$_3$), 121.3 (Ar*C*H), 126.6 (Ar*C*CHN), 128.1 (Ar*C*H), 128.4 (Ar*C*Br), 129.2 (Ar*C*H), 140.5 (Ar*C*N), 148.5 (Ar*C*O), 148.6 (Ar*C*O), 152.8 (Ar*C*O), 156.8 (1C, q, *J* = 36.7, *C*CF$_3$), 157.1 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.5 (3F, s, C*F*$_3$); m/z (ES^-) 596+598 (30%, M^-), 595+597 (100%, M-H^+); HRMS $C_{27}H_{27}(^{79}Br)F_3N_2O_5$ calcd. 595.1055, found 595.0964; Anal. calcd. for $C_{27}H_{28}BrF_3N_2O_5$: C, 54.28; H, 4.72; N, 4.69; found: C, 53.79; H, 4.59; N, 4.47%.

_N_-((1_R_*,2_S_*)-3-(3-(Benzyloxy)-2-bromo-4-methoxyphenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (236s)



236s

Prepared using general procedure L. Crude *β*-nitroamine **230s** (1.15 mmol) afforded crude *β*-aminoacetamide **236s** as a pale brown solid. Purification by flash column chromatography (30% EtOAc/Pet. ether) yielded pure *β*-nitroacetamide **236s** as a white solid (882 mg, 43%, *anti*:*syn* >20:1); mp 68-70 °C; R_f 0.34 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3393 (N-H), 3303 (N-H), 3089-2838 (C-H), 1702 (C=O), 1511 (C=C), 1485, 1454, 1440, 1296, 1271, 1241, 1210 (C-F), 1163 (C-F), 1033 (C-O) cm^{-1}; ^1H NMR (600

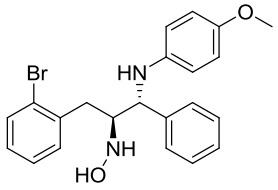
MHz, $CDCl_3$) δ 2.83 (1H, dd, *J* = 14.0, 11.1, C*H*$_2$CHN), 3.13 (1H, dd, *J* = 14.2, 3.5, C*H*$_2$CHN), 3.71 (3H, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 4.36 (1H, br s, N*H*PMP), 4.69-4.74 (2H, m, C*H*NPMP+C*H*NTFA), 4.96 (1H, d, *J* = 10.5, OC*H*$_2$Ph), 5.00 (1H, d, *J* = 10.6, OC*H*$_2$Ph), 6.39 (1H, d, *J* = 9.2, N*H*TFA), 6.55 (2H, d, *J* = 7.3, Ar*H*), 6.72 (2H, d, *J* = 8.8, Ar*H*), 6.80 (1H, d, *J* = 8.5, Ar*H*), 6.85 (1H, d, *J* = 8.5, Ar*H*), 7.33-7.41 (8H, m, Ar*H*), 7.54 (2H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 36.3 (*C*H$_2$CHN), 55.7 (O*C*H$_3$), 55.8 (*C*HNTFA), 56.2 (O*C*H$_3$), 62.2 (*C*HNPMP), 74.7 (O*C*H$_2$Ph), 111.5 (Ar*C*H), 114.9 (Ar*C*H), 115.5 (Ar*C*H), 115.8 (1C, q, *J* = 288.2, *C*F$_3$), 121.1 (Ar*C*CH$_2$), 125.8 (Ar*C*H), 127.4 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 128.9 (Ar*C*Br), 129.1 (Ar*C*H), 137.2 (Ar*C*CH$_2$O), 138.4 (Ar*C*CHN), 140.6 (Ar*C*N), 145.5 (Ar*C*O), 152.7 (Ar*C*O), 152.9 (Ar*C*O), 157.5 (1C, q, *J* = 37.2, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (ES$^-$) 642+644 (1:1, 32%, M$^-$), 641+643 (1:1, 97%, M-H$^+$); HRMS $C_{32}H_{29}(^{79}Br)F_3N_2O_4$ calcd. 641.1263, found 641.1230; Anal. calcd. for $C_{32}H_{30}BrF_3N_2O_4$: C, 59.73; H, 4.35; N, 4.87; found: C, 59.79; H, 4.60; N, 4.34%.

4.4.7 Preparation of *β*-Aminohydroxylamines

General Procedure M

To a solution of crude *β*-nitroamine (1.00 mmol) in THF (5.0 mL) at 0 °C was added MeOH (15.0 mmol) followed by the portionwise addition of freshly amalgamated Al foil (5.00 mmol) [coils of Al foil (~1.00 mmol) were soaked in Et_2O to remove machining oils and individually immersed in sat. $HgCl_{2(aq)}$ solution for 30 s, washed in H_2O for 5 s, roughly dried on tissue and added to the reaction mixture]. The mixture was allowed to warm to rt and rigorously stirred for 2 h to give a dark grey suspension. The mixture was filtered through Celite® and washed with Et_2O (2 x 25 mL) and MeOH (25 mL) and the solvents removed *in vacuo* to give crude *β*-aminohydroxylamine, which was purified by flash column chromatography.

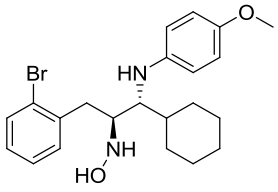
_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-2-(hydroxyamino)-1-phenylpropyl)-4-methoxyaniline (251)



251

Prepared using general procedure M. Crude *β*-nitroamine **230a** (0.478 mmol) afforded crude *β*-aminohydroxylamine **251** as a pale yellow oil. Purification by flash column chromatography (30% EtOAc/Pet. ether) yielded pure *β*-aminohydroxylamine **251** as a pale yellow solid (122 mg, 61%); mp 102-106 °C; R_f 0.30 (30% EtOAc/Pet. ether); IR υ_{max} ($CHCl_3$) 3580 (O-H), 3365 (N-H), 3063-2835 (C-H), 1512 (C=C), 1243 (C-O), 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.78 (1H, dd, *J* = 14.2, 10.8, C*H*$_2$), 2.93 (1H, dd, *J* = 14.2, 3.1, C*H*$_2$), 3.56 (1H, ddd, *J* = 10.7, 4.3, 3.3, C*H*NHOH), 3.71 (3H, s, OC*H*$_3$), 4.41 (1H, br s, N*H*), 4.58 (1H, br s, N*H*), 4.78 (1H, d, *J* = 4.3, C*H*Ph), 6.57 (2H, dm, *J* = 9.0, Ar*H*), 6.72 (2H, dm, *J* = 9.0, Ar*H*), 7.05-7.11 (2H, m, Ar*H*), 7.21 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.27-7.30 (1H, m, Ar*H*), 7.37 (2H, t, *J* = 7.5, Ar*H*), 7.47 (2H, d, *J* = 7.2, Ar*H*), 7.51 (1H, dd, *J* = 7.9, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 33.0 (*C*H$_2$), 55.7 (OC*H*$_3$), 59.6 (*C*HNPMP), 66.5 (*C*HNHOH), 114.7 (Ar*C*H), 115.3 (Ar*C*H), 124.8 (Ar*C*CH$_2$), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 131.3 (Ar*C*H), 133.2 (Ar*C*H), 138.2 (Ar*C*Br), 140.4 (Ar*C*CHN), 141.9 (Ar*C*N), 152.2 (Ar*C*O); m/z (ESI^+) 449+451 (1:1, 9%, M^++Na), 427+429 (1:1, 2%, M^++H), 394+396 (1:1, 3%, M^+-NOH_2), 304+306 (1:1, 100%, M^+-NHPMP); HRMS $C_{22}H_{23}(^{79}Br)N_2O_2Na$ calcd. 449.0835, found 449.0829; Anal. calcd. for $C_{22}H_{23}BrN_2O_2$: C, 61.83; H, 5.42; N, 6.56; found: C, 62.12; H, 5.50; N, 6.34%.

_N_-((1_R_*,2_S_*)-3-(2-Bromophenyl)-1-cyclohexyl-2-(hydroxyamino)propyl)-4-methoxyaniline (278)



278

Prepared using general procedure M. Crude *β*-nitroamine **230f** (0.452 mmol) afforded crude *β*-aminohydroxylamine **278** as a yellow oil. Purification by flash column

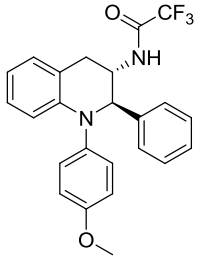
chromatography (30% EtOAc/Pet. ether) yielded pure *β*-aminohydroxylamine **278** as a colourless solid (109 mg, 56%, *anti*:*syn* >20:1); mp 139-141 °C; R_f 0.60 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3356 (O-H), 3242 (N-H), 3056-2850 (C-H), 1509 (C=C), 1233 (C-O), 1037 (C-O), 1024 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (1H, qd, *J* = 12.3, 3.1, Cy*H*), 1.10-1.28 (4H, m, Cy*H*), 1.62-1.68 (2H, m, Cy*H*), 1.71-1.76 (2H, m, Cy*H*), 1.86 (2H, m, Cy*H*), 2.66 (1H, dd, *J* = 14.0, 11.0, CH_2Ar), 2.99 (1H, dd, *J* = 14.0, 3.2, CH_2Ar), 3.17 (1H, br d, *J* = 7.1, N*H*), 3.31 (1H, ddd, *J* = 11.0, 4.3, 3.5, C*H*NHOH), 3.63 (1H, br s, C*H*NPMP), 3.76 (3H, s, OCH_3), 6.72 (2H, dm, *J* = 9.0, Ar*H*), 6.77 (2H, dm, *J* = 9.1, Ar*H*), 7.10 (1H, ddd, *J* = 8.0, 6.8, 2.2, Ar*H*), 7.24-7.28 (2H, m, Ar*H*), 7.55 (1H, dd, *J* = 8.0, 0.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.3 (2 x Cy*C*H_2), 26.5 (Cy*C*H_2), 29.8 (Cy*C*H_2), 31.2 (Cy*C*H_2), 33.2 (*C*H_2Ar), 41.4 (Cy*C*HCHN), 55.9 (O*C*H_3), 59.8 (*C*HNPMP), 63.0 (*C*HNHOH), 114.4 (Ar*C*H), 115.1 (Ar*C*H), 124.8 (Ar*C*CH_2), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 131.9 (Ar*C*H), 133.0 (Ar*C*H), 139.0 (Ar*C*Br), 144.6 (Ar*C*N), 151.8 (Ar*C*O); m/z (CI) 433+435 (1:1, 25%, M^++H), 432+434 (1:1, 18%, M^+), 418+420 (1:1, 42%, M^+-CH_2), 415+417 (1:1, 35%, M^+-OH), 218 (28%, M^+- C_8H_9BrNO); HRMS $C_{22}H_{30}(^{79}Br)N_2O_2$ calcd. 433.1491, found 433.1487; Anal. calcd. for $C_{22}H_{29}BrN_2O_2$: C, 60.97; H, 6.74; N, 6.46; found: C, 61.07; H, 6.79; N, 6.30%.

4.4.8 Preparation of 3-Aminotetrahydroquinolines

General Procedure N

A flame dried Schenk tube was charged with *β*-aminoacetamide (1.00 mmol), $Pd(PPh_3)_4$ (5.00 mol%) and K_2CO_3 (2.50 mmol). The tube was triple evacuated/N_2 filled before the addition of toluene (10.0 mL). The resulting mixture was stirred while N_2 was bubbled through it, using a needle, for 15 min. The N_2 needle was removed and the reaction was heated to 100 °C for 18 h to give a dark brown mixture. The reaction was allowed to cool to rt before being filtered through Celite®, washed with EtOAc and the solvents removed *in vacuo* to give crude tetrahydroquinoline, which was purified by flash column chromatography.

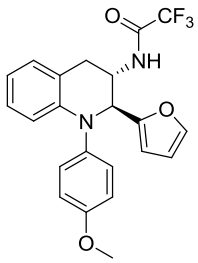
2,2,2-Trifluoro-*N*-[(2*R,3*S**)-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]acetamide (272a)**



272a

Prepared using general procedure N. *β*-Aminoacetamide **236a** (100 mg, 0.197 mmol) afforded crude tetrahydroquinoline **272a** as a brown solid. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272a** as a white solid (82 mg, 98%); mp 162-164 °C; R_f 0.31 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3284 (N-H), 3065-2838 (C-H), 1709 (C=O), 1508 (C=C), 1491, 1456, 1240 (C-O), 1205 (C-F), 1167 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.71 (1H, d, *J* = 17.0, C*H*$_2$), 2.96 (1H, dd, *J* = 17.0, 4.2, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.58 (1H, m, C*H*NH), 4.89 (1H, s, C*H*Ph), 6.66 (1H, br d, *J* = 7.3, N*H*), 6.69 (1H, d, *J* = 8.3, Ar*H*), 6.77 (1H, t, *J* = 7.3, Ar*H*), 6.87 (2H, dm, *J* = 8.7, Ar*H*), 7.05-7.11 (4H, m, Ar*H*), 7.28-7.36 (5H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.7 (*C*H$_2$), 47.6 (*C*HNH), 55.5 (O*C*H$_3$), 66.2 (*C*HPh), 113.7 (Ar*C*H), 115.2 (Ar*C*H), 115.7 (1C, q, *J* = 288.0, *C*F$_3$), 115.8 (Ar*C*CH$_2$), 118.0 (Ar*C*H), 126.4 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (Ar*C*H), 128.9 (Ar*C*H), 130.7 (Ar*C*H), 139.1 (Ar*C*N), 141.0 (Ar*C*CNPMP), 143.7 (Ar*C*N), 156.9 (1C, q, *J* = 37.2, *C*CF$_3$), 157.6 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 427 (22%, $M+H^+$), 426 (100%, M^+); HRMS $C_{24}H_{21}F_3N_2O_2$ calcd. 426.1550, found 426.1539; Anal. calcd. for $C_{24}H_{21}F_3N_2O_2$: C, 67.60; H, 4.96; N, 6.57; found: C, 67.62; H, 4.95; N, 6.57%.

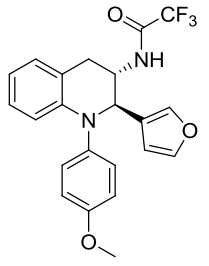
2,2,2-Trifluoro-*N*-[(2*S,3*S**)-2-(furan-2-yl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl]acetamide (272b)**



272b

Prepared using general procedure N. *β*-Aminoacetamide **236b** (107 mg, 0.215 mmol) afforded crude tetrahydroquinoline **272b** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272b** as a white solid (84 mg, 92%); mp 127-130 °C; R_f 0.32 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3414 (N-H), 3300 (N-H), 3073-2838 (C-H), 1710 (C=O), 1509 (C=C), 1492, 1457, 1243 (C-O), 1207 (C-F), 1180 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.79 (1H, d, *J* = 17.2, C*H*$_2$), 3.12 (1H, dd, *J* = 17.1, 4.7, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 4.77 (1H, ddd, *J* = 10.4, 5.1, 2.7, C*H*NTFA), 4.83 (1H, m, C*H*NPMP), 6.19 (1H, dd, *J* = 2.5, 0.7, Furyl-3-*H*), 6.30 (1H, dd, *J* = 3.3, 1.8, Furyl-4-*H*), 6.59 (1H, d, *J* = 8.2, Ar*H*), 6.65 (1H, br d, *J* = 7.7, N*H*TFA), 6.76 (1H, td, *J* = 7.4, 1.0, Ar*H*), 6.89 (2H, dm, *J* = 8.9, Ar*H*), 7.02-7.06 (2H, m, Ar*H*), 7.07 (2H, dm, *J* = 8.9, Ar*H*), 7.38 (1H, dd, *J* = 1.7, 0.7, Furyl-5-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.2 (*C*H$_2$), 45.8 (*C*HNTFA), 55.6 (OC*H*$_3$), 60.8 (*C*HNPMP), 108.4 (Furyl-3-*C*H), 110.5 (Furyl-4-*C*H), 114.5 (Ar*C*H), 115.2 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F$_3$), 116.7 (Ar*C*CH$_2$), 118.6 (Ar*C*H), 127.8 (Ar*C*H), 128.0 (Ar*C*H), 130.6 (Ar*C*H), 138.6 (Ar*C*N), 142.5 (Furyl-5-*C*H), 143.1 (Ar*C*N), 153.0 (Furyl-2-*C*), 156.9 (1C, q, *J* = 37.3, *C*CF$_3$), 157.8 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 417 (28%, M^++H), 416 (100%, M^+), 303 (26%, M^+-NHTFA), 196 (48%, M^+- $C_{22}H_{19}F_3N_2O_3$); HRMS $C_{22}H_{19}F_3N_2O_3$ calcd. 416.1342, found 416.1334; Anal. calcd. for $C_{22}H_{19}F_3N_2O_3$: C, 63.46; H, 4.60; N, 6.73; found: C, 63.44; H, 4.52; N, 6.55%.

2,2,2-Trifluoro-*N*-[(2*R,3*S**)-2-(furan-2-yl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl]acetamide (272c)**

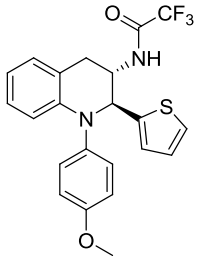


272c

Prepared using general procedure N. *β*-Aminoacetamide **236c** (104 mg, 0.209 mmol) afforded crude tetrahydroquinoline **272c** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272c** as a yellow solid (82 mg, 94%); mp 139-141 °C; R_f 0.70 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3413 (N-H), 3302 (N-H), 3143-2838 (C-H), 1713 (C=O), 1508 (C=C), 1492, 1457, 1242 (C-O),

1207 (C-F), 1160 (C-F), 1036 (C-O), 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (1H, d, *J* = 17.3, C*H*$_2$), 3.14 (1H, dd, *J* = 17.2, 4.8, C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 4.53 (1H, ddd, *J* = 10.4, 5.0, 2.7, C*H*NTFA), 4.73 (1H, t, *J* = 1.4, C*H*NPMP), 6.32 (1H, dd, *J* = 1.6, 0.8, Furyl-4-*H*), 6.64 (1H, d, *J* = 8.1, Ar*H*), 6.64 (1H, br m, N*H*TFA), 6.76 (1H, td, *J* = 7.4, 1.0, Ar*H*), 6.88 (2H, dm, *J* = 9.0, Ar*H*), 7.02-7.06 (2H, m, Ar*H*), 7.09 (2H, dm, *J* = 9.0, Ar*H*), 7.30 (1H, m, Furyl-2-*H*), 7.38 (1H, t, *J* = 1.7, Furyl-5-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.5 (*C*H$_2$), 47.2 (*C*HNTFA), 55.6 (O*C*H$_3$), 59.1 (*C*HNPMP), 108.9 (Furyl-4-*C*H), 114.6 (Ar*C*H), 115.2 (Ar*C*H), 115.8 (1C, q, *J* = 288.1, *C*F$_3$), 116.7 (Ar*C*CH$_2$), 118.6 (Ar*C*H), 125.5 (Furyl-3-*C*CHN), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 130.7 (Ar*C*H), 139.0 (Ar*C*N), 140.6 (Furyl-2-*C*H), 143.0 (Ar*C*N), 143.8 (Furyl-5-*C*H), 156.9 (1C, q, *J* = 37.2, *C*CF$_3$), 157.6 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 416 (6%, M^+), 220 (18%, M^+- $C_7H_7F_3O_3$), 205 (39%, M^+- $C_7H_7F_3NO_3$); HRMS $C_{22}H_{19}F_3N_2O_3$ calcd. 416.1342, found 416.1354; Anal. calcd. for $C_{22}H_{19}F_3N_2O_3$: C, 63.46; H, 4.60; N, 6.73; found: C, 63.33; H, 4.54; N, 6.64%.

2,2,2-Trifluoro-*N*-((2*S,3*S**)-1-(4-methoxyphenyl)-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272d)**

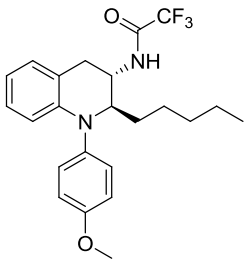


272d

Prepared using general procedure N. *β*-Aminoacetamide **236d** (102 mg, 0.199 mmol) afforded crude tetrahydroquinoline **272d** as a brown oil. Purification by flash column chromatography (20% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272d** as an off-white solid (79 mg, 92%); mp 134-136 °C; R_f 0.41 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3413 (N-H), 3295 (N-H), 3075-2838 (C-H), 1709 (C=O), 1508 (C=C), 1491, 1456, 1242 (C-O), 1206 (C-F), 1168 (C-F), 1036 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.78 (1H, d, *J* = 17.3, C*H*$_2$), 3.18 (1H, dd, *J* = 17.2, 4.7, C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 4.63 (1H, m, C*H*NTFA), 5.06 (1H, m, C*H*NPMP), 6.64 (1H, br d, *J* = 7.6, N*H*TFA), 6.67 (1H, d, *J* = 7.9, Ar*H*), 6.79 (1H, td, *J* = 7.4, 1.0, Ar*H*), 6.88 (2H, dm, *J* = 8.9, Ar*H*), 6.95-6.97 (2H, m, Thiophenyl-3,4-*H*), 7.07 (2H, m, Ar*H*), 7.12 (2H, dm, *J* = 9.0, Ar*H*), 7.22 (1H, dd, *J* = 4.8,

1.4, Thiophenyl-5-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.3 (*C*H_2), 48.1 (*C*HNTFA), 55.6 (O*C*H_3), 62.5 (*C*HNPMP), 114.9 (Ar*C*H), 115.2 (Ar*C*H), 115.8 (1C, q, *J* = 288.1, *C*F_3), 116.5 (Ar*C*CH_2), 118.8 (Ar*C*H), 125.0 (Thiophenyl-5-*C*H), 125.1 (Thiophenyl-3-*C*H), 127.3 (Thiophenyl-4-*C*H), 127.6 (Ar*C*H), 128.0 (Ar*C*H), 130.7 (Ar*C*H), 139.0 (Ar*C*N), 142.8 (Ar*C*HNPMP), 144.3 (Thiophenyl-2-*C*), 157.0 (1C, q, *J* = 37.4, *C*CF_3), 157.7 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 432 (18%, M^+); HRMS $C_{22}H_{19}F_3N_2O_2S$ calcd. 432.1114, found 432.1116; Anal. calcd. for $C_{22}H_{19}F_3N_2O_2S$: C, 61.10; H, 4.43; N, 6.48; found: C, 61.15; H, 4.38; N, 6.42%.

2,2,2-Trifluoro-*N*-((2*R,3*S**)-1-(4-methoxyphenyl)-2-pentyl-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272e)**

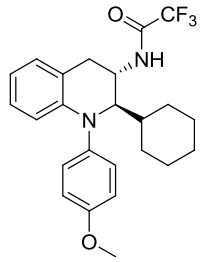


272e

Prepared using general procedure N. *β*-Aminoacetamide **236e** (187 mg, 0.373 mmol) afforded crude tetrahydroquinoline **272e** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272e** as a white solid (137 mg, 87%); mp 93-94 °C; R_f 0.50 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3415 (N-H), 3292 (N-H), 3066-2860 (C-H), 1712 (C=O), 1507 (C=C), 1492, 1456, 1242 (C-O), 1204 (C-F), 1157 (C-F), 1037 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8, $(CH_2)_4CH_3$), 1.22-1.45 (6H, m, $CH_2(CH_2)_3CH_3$), 1.52 (1H, dddd, *J* = 19.3, 14.3, 10.0, 5.1, $CH_2(CH_2)_3CH_3$), 1.75 (1H, dddd, *J* = 16.4, 13.9, 11.0, 5.5, $CH_2(CH_2)_3CH_3$), 2.82 (1H, d, *J* = 17.3, CH_2Ar), 3.23 (1H, dd, *J* = 17.3, 4.7, CH_2Ar), 3.56 (1H, m, C*H*NPMP), 3.84 (3H, s, OCH_3), 4.50 (1H, m, C*H*NTFA), 6.57 (1H, d, *J* = 8.3, Ar*H*), 6.64 (1H, br d, *J* = 7.3, N*H*TFA), 6.74 (1H, t, *J* = 7.3, Ar*H*), 6.94 (2H, dm, *J* = 8.6, Ar*H*), 6.99 (1H, t, *J* = 7.7, Ar*H*), 7.07 (1H, d, *J* = 7.4, Ar*H*), 7.11 (2H, dm, *J* = 8.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 22.6 (CH_2CH_3), 25.2 ($CH_2CH_2CH_3$), 28.2 (CH_2Ar), 31.7 ($CH_2(CH_2)_2CH_3$), 31.8 (CH_2CHN), 44.8 (*C*NHTFA), 55.6 (O*C*H_3), 62.7 (*C*HNPMP), 115.3 (Ar*C*H), 115.5 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F_3), 117.0 (Ar*C*CH_2), 118.4 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 130.6 (Ar*C*H), 139.3 (Ar*C*N), 142.6 (Ar*C*N), 156.7 (1C, q, *J*

= 37.1, *C*CF_3), 157.4 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 420 (10%, M^+), 349 (100%, M^+-^{n}pentyl); HRMS $C_{23}H_{27}F_3N_2O_2$ calcd. 420.2019, found 420.2002; Anal. calcd. for $C_{23}H_{27}F_3N_2O_2$: C, 65.70; H, 6.47; N, 6.66; found: C, 65.93; H, 6.51; N, 6.67%.

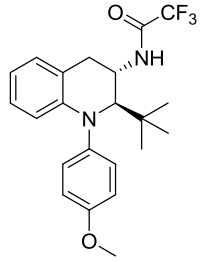
_N_-((2_R_*,3_S_*)-2-Cyclohexyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (272f)



272f

Prepared using general procedure N except with 10 mol% $Pd(PPh_3)_4$. *β*-Aminoacetamide **236f** (63 mg, 0.12 mmol) afforded crude tetrahydroquinoline **272f** as a pale brown oil. Purification by flash column chromatography (20% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272f** as an off-white solid (43 mg, 81%); mp 95-97 °C; R_f 0.46 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3410 (N-H), 3304 (N-H), 3067-2852 (C-H), 1721 (C=O), 1506 (C=C), 1491, 1456, 1272, 1244 (C-O), 1229, 1203 (C-F), 1174 (C-F), 1037 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.10-1.26 (5H, m, Cy*H*), 1.39-1.46 (1H, m, Cy*H*), 1.69 (1H, m, Cy*H*), 1.78-1.86 (3H, m, Cy*H*), 2.10 (1H, d, *J* = 12.1, Cy*H*), 2.86 (1H, d, *J* = 17.8, C*H*$_2$Ar), 3.16 (1H, dd, *J* = 17.8, 5.5, C*H*$_2$Ar), 3.48 (1H, dd, *J* = 10.0, 2.2, C*H*NPMP), 3.80 (3H, s, OC*H*$_3$), 4.62 (1H, m, C*H*NTFA), 6.53 (1H, br d, *J* = 7.0, N*H*TFA), 6.83 (2H, dm, *J* = 9.0, Ar*H*), 6.86 (1H, td, *J* = 7.4, 0.9, Ar*H*), 6.94 (1H, d, *J* = 8.1, Ar*H*), 7.06 (1H, td, *J* = 7.7, 0.9, Ar*H*), 7.11-7.13 (3H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.3 (Cy*C*H$_2$), 26.3 (Cy*C*H$_2$), 26.5 (Cy*C*H$_2$), 28.7 (*C*H$_2$Ar), 29.5 (Cy*C*H$_2$), 31.7 (Cy*C*H$_2$), 39.0 (Cy*C*HCHN), 45.5 (*C*HNTFA), 55.7 (O*C*H$_3$), 67.2 (*C*HNPMP), 115.1 (Ar*C*H), 115.6 (1C, q, *J* = 288.2, *C*F_3), 120.4 (Ar*C*H), 120.5 (Ar*C*H), 120.9 (Ar*C*CH$_2$), 123.5 (Ar*C*H), 127.3 (Ar*C*H), 130.6 (Ar*C*H), 141.5 (Ar*C*N), 143.3 (Ar*C*N), 155.5 (Ar*C*O), 156.5 (1C, q, *J* = 37.0, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$); m/z (CI) 433 (100%, M^++H), 432 (44%, M^+), 349 (32%, M^+-Cy); HRMS $C_{24}H_{28}F_3N_2O_2$ calcd. 433.2103, found 433.2115; Anal. calcd. for $C_{24}H_{27}F_3N_2O_2$: C, 66.65; H, 6.29; N, 6.48; found: C, 66.64; H, 6.49; N, 6.16%.

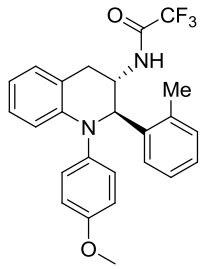
_N_-((2_R_*,3_S_*)-2-(_tert_-Butyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (272g)



272g

Prepared using general procedure N. *β*-Aminoacetamide **236g** (94 mg, 0.19 mmol) afforded crude tetrahydroquinoline **272g** as a dark brown oil. Purification by flash column chromatography (20% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272g** as a white solid (48 mg, 61%); mp 119-121 °C; R_f 0.46 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3291 (N-H), 3080-2838 (C-H), 1712 (C=O), 1507 (C=C), 1491, 1456, 1243 (C-O), 1205 (C-F), 1157 (C-F), 1038 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00 (9H, s, C(CH_3)$_3$), 2.83 (1H, d, *J* = 7.6, CH_2), 3.27 (1H, dd, *J* = 17.5, 5.2, CH_2), 3.57 (1H, t, *J* = 1.8, C*H*NPMP), 3.81 (3H, s, OCH_3), 4.75 (1H, td, *J* = 5.4, 2.5, C*H*NTFA), 6.46 (1H, br d, *J* = 7.0, N*H*), 6.78-6.80 (2H, m, Ar*H*), 6.88 (2H, dm, *J* = 8.9, Ar*H*), 7.02 (1H, t, *J* = 7.7, Ar*H*), 7.07 (1H, d, *J* = 7.6, Ar*H*), 7.12 (2H, dm, *J* = 8.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.6 (C(*C*H_3)$_3$), 30.0 (*C*H_2), 36.9 (*C*(CH$_3$)$_3$), 45.0 (*C*HNPMP), 55.6 (O*C*H_3), 71.2 (*C*HNTFA), 115.0 (Ar*C*H), 115.7 (1C, q, *J* = 288.1, *C*F_3), 117.4 (Ar*C*H), 118.4 (Ar*C*CH$_2$), 119.3 (Ar*C*H), 126.8 (Ar*C*H), 127.7 (Ar*C*H), 130.6 (Ar*C*H), 142.7 (Ar*C*N), 143.8 (Ar*C*N), 156.4 (1C, q, *J* = 37.1, C*C*F_3), 156.5 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (CI) 407 (100%, M^++H), 407 (12%, M^+), 349 (17%, M^+-C(CH$_3$)$_3$); HRMS $C_{22}H_{26}F_3N_2O_2$ calcd. 407.1946, found 407.1953; Anal. calcd. for $C_{22}H_{25}F_3N_2O_2$: C, 65.01; H, 6.20; N, 6.89; found: C, 64.75; H, 6.23; N, 6.61%.

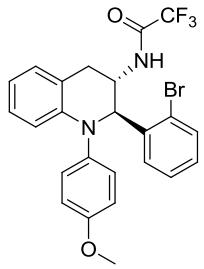
2,2,2-Trifluoro-*N*-((2*R,3*S**)-1-(4-methoxyphenyl)-2-(*o*-tolyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272h)**



272h

Prepared using general procedure N. *β*-Aminoacetamide **236h** (114 mg, 0.219 mmol) afforded crude tetrahydroquinoline **272h** as a brown oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272h** as an orange solid (85 mg, 88%); mp 62-65 °C; R_f 0.67 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3285 (N-H), 3063-2838 (C-H), 1719 (C=O), 1601, 1528, 1508 (C=C), 1491, 1456, 1280, 1239 (C-O), 1206 (C-F), 1166 (C-F), 1035 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.48 (3H, s, ArC*H*$_3$), 2.71 (1H, d, *J* = 16.9, C*H*$_2$), 3.07 (1H, dd, *J* = 16.9, 3.4, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.51 (1H, m, C*H*NTFA), 5.03 (1H, d, *J* = 1.3, C*H*NPMP), 6.61 (1H, d, *J* = 8.4, Ar*H*), 6.65 (1H, br d, *J* = 6.4, N*H*), 6.77 (1H, t, *J* = 7.4, Ar*H*), 6.87 (2H, br d, *J* = 7.8, Ar*H*), 7.04 (2H, br d, *J* = 8.1, Ar*H*), 7.08-7.10 (2H, m, Ar*H*), 7.15 (1H, t, *J* = 7.3, Ar*H*), 7.19-7.23 (2H, m, Ar*H*), 7.35 (1H, d, *J* = 7.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.0 (*C*H$_3$Ar), 27.9 (*C*H$_2$), 45.6 (*C*HNTFA), 55.5 (O*C*H$_3$), 64.1 (*C*HNPMP), 113.2 (Ar*C*H), 114.9 (Ar*C*CH$_2$), 115.3 (Ar*C*H), 115.9 (1C, q, *J* = 288.1, *C*F$_3$), 117.7 (Ar*C*H), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 127.8 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 130.8 (Ar*C*H), 131.2 (Ar*C*H), 135.1 (Ar*C*CH$_3$), 139.1 (Ar*C*CNPMP), 139.1 (Ar*C*N), 144.5 (Ar*C*N), 157.2 (1C, q, *J* = 37.2, *C*CF$_3$), 157.9 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.1 (3F, s, C*F*$_3$); m/z (EI) 441 (27%, M^++H), 440 (100%, M^+); HRMS $C_{25}H_{23}F_3N_2O_2$ calcd. 440.1706, found 440.1712; Anal. calcd. for $C_{25}H_{23}F_3N_2O_2$: C, 68.17; H, 5.26; N, 6.36; found: C, 67.84; H, 5.23; N, 6.36%.

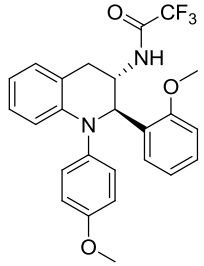
_N_-((2_R_*,3_S_*)-2-(2-Bromophenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (272i)



272i

Prepared using general procedure N. *β*-Aminoacetamide **236i** (90 mg, 0.15 mmol) afforded crude tetrahydroquinoline **272i** as a brown oil. Purification by flash column chromatography (20% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272i** as a white solid (42 mg, 54%); mp 145-146 °C; R_f 0.36 (10% Et_2O/Pet. ether); IR υ_{max} (neat) 3421 (N-H), 3311 (N-H), 3065-2838 (C-H), 1725 (C=O), 1508 (C=C), 1491, 1457, 1240 (C-O), 1205 (C-F), 1167 (C-F), 1036 (C-O), 1023 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.77 (1H, d, *J* = 17.0, C*H*$_2$), 2.91 (1H, dd, *J* = 17.0, 4.1, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.84 (1H, app dt, *J* = 11.3, 3.4, C*H*NTFA), 5.09 (1H, s, C*H*NPMP), 6.59 (1H, br d, *J* = 8.0, N*H*), 6.65 (1H, d, *J* = 8.2, Ar*H*), 6.79 (1H, td, *J* = 7.3, 0.5, Ar*H*), 6.87 (2H, d, *J* = 8.9, Ar*H*), 7.03 (2H, d, *J* = 8.6, Ar*H*), 7.07 (1H, d, *J* = 7.4, Ar*H*), 7.08 (1H, t, *J* = 7.8, Ar*H*), 7.17 (1H, td, *J* = 7.7, 1.6, Ar*H*), 7.25 (1H, td, *J* = 7.6, 0.8, Ar*H*), 7.41 (1H, dd, *J* = 7.8, 1.4, Ar*H*), 7.57 (1H, dd, *J* = 7.9, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.4 (*C*H_2), 44.9 (*C*HNTFA), 55.6 (O*C*H_3), 66.7 (*C*HNPMP), 113.6 (Ar*C*H), 115.4 (Ar*C*H), 115.8 (Ar*C*CH_2), 115.9 (1C, q, *J* = 288.3, *C*F_3), 118.5 (Ar*C*H), 122.0 (Ar*C*Br), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 129.7 (Ar*C*H), 130.9 (Ar*C*H), 133.7 (Ar*C*H), 138.6 (Ar*C*N), 139.4 (Ar*C*CNPMP), 143.8 (Ar*C*N), 156.7 (1C, q, *J* = 37.1, *C*CF_3), 157.9 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.1 (3F, s, C*F*$_3$); m/z (CI) 506+508 (1:1, 29%, M^++H_2), 505+507 (1:1, 100%, M^++H), 504+506 (1:1, 8%, M^+); HRMS $C_{24}H_{21}(^{79}Br)F_3N_2O_2$ calcd. 505.0739, found 505.0746; Anal. calcd. for $C_{24}H_{20}BrF_3N_2O_2$: C, 57.04; H, 3.99; N, 5.54; found: C, 57.17; H, 3.84; N, 5.73%.

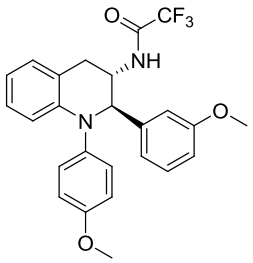
2,2,2-Trifluoro-*N*-((2*R,3*S**)-2-(2-methoxyphenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272j)**



272j

Prepared using general procedure N. *β*-Aminoacetamide **236j** (113 mg, 0.210 mmol) afforded crude tetrahydroquinoline **272j** as a brown solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272j** as an orange solid (94 mg, 98%); mp 168-170 °C; R_f 0.63 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3417 (N-H), 3313 (N-H), 3069-2838 (C-H), 1722 (C=O), 1600, 1508 (C=C), 1488, 1456, 1283, 1238, 1202 (C-F), 1160 (C-F), 1097, 1031 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.72 (1H, d, *J* = 17.0, C*H*$_2$), 2.87 (1H, dd, *J* = 16.9, 4.2, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 4.79 (1H, m, C*H*NTFA), 5.09 (1H, s, C*H*NPMP), 6.65 (1H, d, *J* = 7.9, N*H*), 6.69 (1H, d, *J* = 8.3, Ar*H*), 6.76 (1H, t, *J* = 7.3, Ar*H*), 6.85-6.89 (3H, m, Ar*H*), 6.90 (1H, d, *J* = 8.1, Ar*H*), 7.03 (1H, d, *J* = 7.4, Ar*H*), 7.06-7.10 (3H, m, Ar*H*), 7.26-7.29 (2H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.8 (*C*H$_2$), 44.9 (*C*HNTFA), 55.4 (OCH_3), 55.6 (OCH_3), 62.2 (*C*HNPMP), 110.6 (Ar*C*H), 113.6 (Ar*C*H), 115.2 (Ar*C*H), 115.9 (1C, q, *J* = 288.2, *C*F$_3$), 116.3 (Ar*C*CH$_2$), 118.1 (Ar*C*H), 120.6 (Ar*C*H), 127.6 (Ar*C*H), 127.9 (2 x Ar*C*H), 128.4 (Ar*C*CNPMP), 129.0 (Ar*C*H), 130.8 (Ar*C*H), 139.3 (Ar*C*N), 144.0 (Ar*C*N), 155.9 (Ar*C*O), 156.7 (1C, q, *J* = 36.8, *C*CF$_3$), 157.6 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 457 (27%, M^++H), 456 (100%, M^+), 342 (37%, M^+-$C_3H_5F_3O$); HRMS $C_{25}H_{23}F_3N_2O_3$ calcd. 456.1655, found 456.1659; Anal. calcd. for $C_{25}H_{23}F_3N_2O_3$: C, 65.78; H, 5.08; N, 6.14; found: C, 65.55; H, 5.01; N, 6.03%.

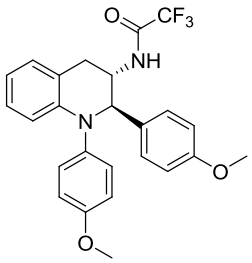
2,2,2-Trifluoro-*N*-((2*R,3*S**)-2-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272k)**



272k

Prepared using general procedure N. *β*-Aminoacetamide **236k** (130 mg, 0.242 mmol) afforded crude tetrahydroquinoline **272k** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272k** as a white solid (99 mg, 90%); mp 114-116 °C; R_f 0.38 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3306 (N-H), 3069-2837 (C-H), 1712 (C=O), 1601, 1508 (C=C), 1489, 1456, 1278, 1238, 1205 (C-F), 1151 (C-F), 1037 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.70 (1H, d, *J* = 17.0, C*H*$_2$), 2.97 (1H, dd, *J* = 17.0, 4.2, C*H*$_2$), 3.75 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.59 (1H, m, C*H*NTFA), 4.85 (1H, s, C*H*NPMP), 6.66-6.68 (1H, br m, N*H*), 6.68 (1H, d, *J* = 8.3, Ar*H*), 6.75 (1H, t, *J* = 7.4, Ar*H*), 6.83 (1H, dd, *J* = 8.2, 2.2, Ar*H*), 6.86-6.88 (3H, m, Ar*H*), 6.95 (1H, d, *J* = 7.6, Ar*H*), 7.06 (2H, t, *J* = 8.3, Ar*H*), 7.09 (2H, d, *J* = 8.2, Ar*H*), 7.26 (1H, t, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.9 (*C*H$_2$), 47.7 (*C*HNTFA), 55.3 (O*C*H$_3$), 55.6 (O*C*H$_3$), 66.2 (*C*HNPMP), 112.3 (Ar*C*H), 113.0 (Ar*C*H), 113.9 (Ar*C*H), 115.3 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F$_3$), 116.0 (Ar*C*CH$_2$), 118.1 (Ar*C*H), 118.7 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (Ar*C*H), 130.1 (Ar*C*H), 130.8 (Ar*C*H), 139.2 (Ar*C*N), 142.8 (Ar*C*CNPMP), 143.7 (Ar*C*N), 157.0 (1C, q, *J* = 37.2, *C*CF$_3$), 157.6 (Ar*C*O), 160.0 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 457 (28%, M^++H), 456 (100%, M^+), 342 (68%, M^+-$C_3H_5F_3O$), 236 (47%, M^+- $C_9H_9F_3NO_2$); HRMS $C_{25}H_{23}F_3N_2O_3$ calcd. 456.1655, found 456.1652; Anal. calcd. for $C_{25}H_{23}F_3N_2O_3$: C, 65.78; H, 5.08; N, 6.14; found: C, 65.98; H, 5.23; N, 5.96%.

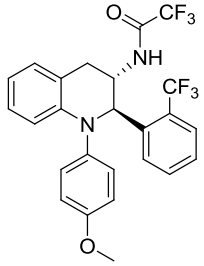
2,2,2-Trifluoro-*N*-((2*R,3*S**)-2-(4-methoxyphenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272l)**



272l

Prepared using general procedure N. *β*-Aminoacetamide **236l** (123 mg, 0.229 mmol) afforded crude tetrahydroquinoline **272l** as a brown oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272l** as an orange solid (102 mg, 98%); mp 118-120 °C; R_f 0.51 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3300 (N-H), 3067-2837 (C-H), 1709 (C=O), 1608, 1508 (C=C), 1491, 1456, 1240 (C-O), 1206 (C-F), 1170 (C-F), 1105, 1032 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.69 (1H, d, *J* = 17.0, C*H*$_2$), 2.97 (1H, dd, *J* = 17.0, 4.4, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 4.52 (1H, m, C*H*NTFA), 4.80 (1H, s, C*H*NPMP), 6.62 (1H, br d, *J* = 7.7, N*H*), 6.66 (1H, d, *J* = 8.3, Ar*H*), 6.75 (1H, t, *J* = 7.4, Ar*H*), 6.85-6.87 (4H, m, Ar*H*), 7.04-7.08 (4H, m, Ar*H*), 7.24 (2H, dm, *J* = 8.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.7 (*C*H$_2$), 47.8 (*C*HNTFA), 55.4 (O*C*H$_3$), 55.6 (O*C*H$_3$), 65.8 (*C*HNPMP), 113.8 (Ar*C*H), 114.3 (Ar*C*H), 115.2 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F$_3$), 116.0 (Ar*C*CH$_2$), 118.0 (Ar*C*H), 127.6 (Ar*C*H), 128.0 (Ar*C*H), 128.1 (Ar*C*H), 130.8 (Ar*C*H), 133.0 (Ar*C*CNPMP), 139.1 (Ar*C*N), 143.8 (Ar*C*N), 157.0 (1C, q, *J* = 37.2, *C*CF$_3$), 157.6 (Ar*C*O), 159.2 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, C*F*$_3$); m/z (EI) 457 (27%, M^++H), 456 (100%, M^+), 342 (42%, M^+-$C_3H_5F_3O$); HRMS $C_{25}H_{23}F_3N_2O_3$ calcd. 456.1655, found 456.1662; Anal. calcd. for $C_{25}H_{23}F_3N_2O_3$: C, 65.78; H, 5.08; N, 6.14; found: C, 65.88; H, 5.04; N, 6.14%.

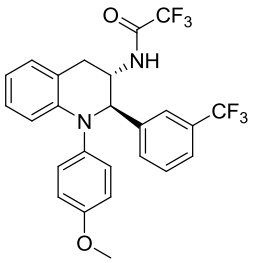
2,2,2-Trifluoro-*N*-((2*R,3*S**)-1-(4-methoxyphenyl)-2-(2-trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272m)**



272m

Prepared using general procedure N. *β*-Aminoacetamide **236m** (85 mg, 0.15 mmol) afforded crude tetrahydroquinoline **272m** as a pale brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272m** as a white solid (71 mg, 97%); mp 176-178 °C; R_f 0.31 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3418 (N-H), 3312 (N-H), 3075-2855 (C-H), 1726 (C=O), 1509 (C=C), 1492, 1457, 1311, 1280, 1245, 1209 (C-F), 1157 (C-F), 1122 (C-F), 1105 (C-F), 1037 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.85 (1H, dd, *J* = 16.9, 2.3, C*H*$_2$), 3.10 (1H, dd, *J* = 16.9, 4.0, C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 4.69 (1H, app dt, *J* = 12.0, 3.6, C*H*NTFA), 5.15 (1H, d, *J* = 2.0, C*H*NPMP), 6.57 (2H, d, *J* = 8.3, N*H*TFA + Ar*H*), 6.80 (1H, td, *J* = 7.4, 0.7, Ar*H*), 6.84 (2H, d, *J* = 8.8, Ar*H*), 6.96 (2H, d, *J* = 8.2, Ar*H*), 7.08 (1H, t, *J* = 7.8, Ar*H*), 7.11 (1H, d, *J* = 7.4, Ar*H*), 7.41 (1H, t, *J* = 7.6, Ar*H*), 7.51 (1H, t, *J* = 7.6, Ar*H*), 7.64 (1H, d, *J* = 7.9, Ar*H*), 7.66 (1H, d, *J* = 7.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.5 (*C*H_2), 46.6 (*C*HNTFA), 55.5 (O*C*H_3), 63.4 (*C*HNPMP), 113.7 (Ar*C*H), 115.3 (Ar*C*H), 115.8 (1C, q, *J* = 288.2, CO*C*F_3), 116.0 (Ar*C*CH_2), 118.5 (Ar*C*H), 124.2 (1C, q, *J* = 274.3, *C*F_3Ar), 126.6 (1C, q, *J* = 5.9, Ar*C*H), 127.8 (1C, q, *J* = 30.3, Ar*C*CF_3), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 129.0 (Ar*C*H), 130.9 (Ar*C*H), 132.3 (Ar*C*H), 138.0 (Ar*C*N), 139.9 (Ar*C*CNPMP), 144.3 (Ar*C*N), 156.4 (1C, q, *J* = 37.2, *C*OCF_3), 158.0 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, COC*F*$_3$), -58.6 (3F, s, ArC*F*$_3$); m/z (EI) 494 (30%, M^+), 380 (100%, M^+-$C_3H_5F_3O$), 236 (62%, M^+-$C_9H_6F_6NO$); HRMS $C_{25}H_{20}F_6N_2O_2$ calcd. 494.1424, found 494.1428; Anal. calcd. for $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67; found: C, 60.58; H, 3.76; N, 5.58%.

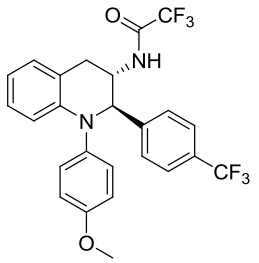
2,2,2-Trifluoro-*N*-((2*R,3*S**)-1-(4-methoxyphenyl)-2-(3-trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272n)**



272n

Prepared using general procedure N. *β*-Aminoacetamide **236n** (119 mg, 0.207 mmol) afforded crude tetrahydroquinoline **272n** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272n** as a white solid (101 mg, 99%); mp 169-171 °C; R_f 0.32 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3419 (N-H), 3301 (N-H), 3072-2840 (C-H), 1710 (C=O), 1508 (C=C), 1492, 1458, 1328, 1316, 1242, 1205 (C-F), 1163 (C-F), 1125 (C-F), 1074, 1038 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.72 (1H, d, *J* = 17.1, C*H*$_2$), 2.91 (1H, dd, *J* = 17.0, 4.3, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.57 (1H, m, C*H*NTFA), 4.96 (1H, s, C*H*NPMP), 6.60 (1H, br d, *J* = 7.4, N*H*TFA), 6.67 (1H, d, *J* = 8.2, Ar*H*), 6.79 (1H, td, *J* = 7.4, 0.9, Ar*H*), 6.87 (2H, dm, *J* = 8.9, Ar*H*), 7.02 (2H, dm, *J* = 8.8, Ar*H*), 7.07 (1H, d, *J* = 7.5, Ar*H*), 7.10 (1H, t, *J* = 8.3, Ar*H*), 7.47 (1H, t, *J* = 7.7, Ar*H*), 7.56-7.57 (2H, m, Ar*H*), 7.60 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.6 (*C*H$_2$), 47.6 (*C*HNTFA), 55.6 (O*C*H$_3$), 66.0 (*C*HNPMP), 114.1 (Ar*C*H), 115.4 (Ar*C*H), 115.5 (Ar*C*CH$_2$), 115.7 (1C, q, *J* = 287.9, CO*C*F$_3$), 118.5 (Ar*C*H), 123.4 (1C, q, *J* = 3.5, Ar*C*H), 124.0 (1C, q, *J* = 272.5, *C*F$_3$Ar), 124.9 (1C, q, *J* = 3.7, Ar*C*H), 128.1 (Ar*C*H), 128.4 (Ar*C*H), 129.6 (Ar*C*H), 130.0 (Ar*C*H), 130.8 (Ar*C*H), 131.4 (1C, q, *J* = 32.5, Ar*C*CF$_3$), 138.8 (Ar*C*N), 142.2 (Ar*C*CNPMP), 143.5 (Ar*C*N), 157.1 (1C, q, *J* = 37.5, *C*OCF$_3$), 157.9 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, COC*F*$_3$), -63.0 (3F, s, ArC*F*$_3$); m/z (CI) 496 (23%, M^++H_2), 495 (100%, M^++H), 494 (45%, M^+); HRMS $C_{25}H_{21}F_6N_2O_2$ calcd. 495.1507, found 495.1490; Anal. calcd. for $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67; found: C, 60.62; H, 4.08; N, 5.57%.

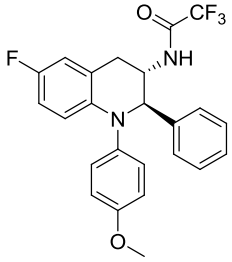
2,2,2-Trifluoro-*N*-((2*R,3*S**)-1-(4-methoxyphenyl)-2-(4-trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (272o)**



272o

Prepared using general procedure N. *β*-Aminoacetamide **236o** (139 mg, 0.242 mmol) afforded crude tetrahydroquinoline **272o** as a brown oil. Purification by flash column chromatography (20% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272o** as an off-white solid (118 mg, 99%); mp 162-164 °C; R_f 0.41 (20% Et_2O/Pet. ether); IR υ_{max} (neat) 3417 (N-H), 3281 (N-H), 3069-2848 (C-H), 1710 (C=O), 1509 (C=C), 1492, 1457, 1323, 1244 (C-O), 1208 (C-F), 1164 (C-F), 1124 (C-F), 1106, 1067, 1037 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.72 (1H, d, *J* = 17.2, C*H*$_2$), 2.90 (1H, dd, *J* = 17.1, 4.1, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.56 (1H, m, C*H*NTFA), 4.95 (1H, s, C*H*NPMP), 6.62 (1H, br d, *J* = 6.6, N*H*), 6.68 (1H, d, *J* = 8.3, Ar*H*), 6.79 (1H, t, *J* = 7.4, Ar*H*), 6.87 (2H, d, *J* = 8.8, Ar*H*), 7.03 (2H, d, *J* = 8.5, Ar*H*), 7.07 (1H, d, *J* = 7.4, Ar*H*), 7.10 (1H, t, *J* = 7.9, Ar*H*), 7.49 (2H, d, *J* = 8.0, Ar*H*), 7.61 (2H, d, *J* = 8.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.6 (*C*H_2), 47.5 (*C*HNTFA), 55.6 (O*C*H_3), 66.0 (*C*HNPMP), 114.1 (Ar*C*H), 115.4 (Ar*C*H), 115.5 (Ar*C*CH_2), 115.7 (1C, q, *J* = 287.8, CO*C*F_3), 118.5 (Ar*C*H), 124.1 (1C, q, *J* = 272.1, *C*F_3Ar), 126.0 (1C, q, *J* = 3.6, Ar*C*H), 127.0 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 130.2 (1C, q, *J* = 32.6, Ar*C*CF_3), 130.8 (Ar*C*H), 138.8 (Ar*C*N), 143.5 (Ar*C*N), 145.1 (Ar*C*CNPMP), 157.1 (1C, q, *J* = 37.5, *C*OCF_3), 157.9 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (3F, s, COC*F*$_3$), -63.0 (3F, s, ArC*F*$_3$); m/z (CI) 496 (28%, M^++H_2), 495 (100%, M^++H), 494 (17%, M^+), 406 (52%), 280 (32%); HRMS $C_{25}H_{21}F_6N_2O_2$ calcd. 495.1507, found 495.1512; Anal. calcd. for $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67; found: C, 60.68; H, 3.98; N, 5.63%.

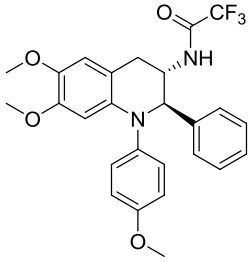
2,2,2-Trifluoro-*N*-[(2*R,3*S**)-6-fluoro-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]acetamide (272p)**



272p

Prepared using general procedure N. *β*-Aminoacetamide **236p** (115 mg, 0.219 mmol) afforded crude tetrahydroquinoline **272p** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272p** as a white solid (91 mg, 93%); mp 112-124 °C; R_f 0.35 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3416 (N-H), 3291 (N-H), 3066-2838 (C-H), 1709 (C=O), 1508 (C=C), 1497, 1243 (C-O), 1209 (C-F), 1178 (C-F), 1034 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.68 (1H, d, *J* = 17.3, C*H*$_2$), 2.90 (1H, dd, *J* = 17.2, 4.2, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 4.58 (1H, m, C*H*NTFA), 4.85 (1H, s, C*H*Ph), 6.61 (1H, br d, *J* = 7.5, N*H*), 6.65 (1H, dd, *J* = 9.0, 4.8, Ar*H*), 6.77-6.82 (2H, m, Ar*H*), 6.85 (2H, dm, *J* = 8.9, Ar*H*), 7.05 (2H, dm, *J* = 8.8, Ar*H*), 7.28-7.36 (5H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.1 (*C*H_2), 47.6 (*C*HNH), 55.6 (O*C*H_3), 66.1 (*C*HPh), 115.0 (1C, d, *J* = 22.2, Ar*C*H), 115.0 (1C, d, *J* = 7.3, Ar*C*H), 115.3 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F_3), 116.7 (1C, d, *J* = 22.3, Ar*C*H), 117.5 (1C, d, *J* = 7.0, Ar*C*CH_2), 126.3 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 129.0 (Ar*C*H), 139.4 (Ar*C*N), 139.9 (1C, d, *J* = 1.6, Ar*C*N), 140.7 (Ar*C*CNPMP), 155.8 (1C, d, *J* = 237.3, Ar*C*F), 157.0 (1C, q, *J* = 37.3, *C*CF_3), 157.6 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -127.4 (1H, m, Ar*F*), -76.2 (3F, s, C*F*$_3$); m/z (EI) 445 (23%, M^++H), 444 (100%, M^+), 330 (53%, M^+-$C_3H_5F_3O$), 254 (33% M^+-$C_8H_7F_3NO$); HRMS $C_{24}H_{20}F_4N_2O_2$ calcd. 444.1455, found 444.1459; Anal. calcd. for $C_{24}H_{20}F_4N_2O_2$: C, 64.86; H, 4.54; N, 6.30; found: C, 64.94; H, 4.57; N, 6.15%.

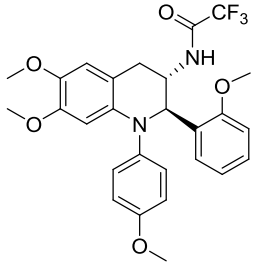
***N*-[(2*R**,3*S**)-6,7-Dimethoxy-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]-2,2,2-trifluoroacetamide (272q)**



272q

Prepared using general procedure N. *β*-Aminoacetamide **XX** (49 mg, 86 μmol) afforded crude tetrahydroquinoline **272q** as a brown oil. Purification by flash column chromatography (50% Et_2O/Pet. ether) yielded pure tetrahydroquinoline **272q** as a white solid (38 mg, 91%); mp 136-138 °C; R_f 0.40 (50% Et_2O/Pet. ether); IR υ_{max} (neat) 3416 (N-H), 3292 (N-H), 3064-2836 (C-H), 1709 (C=O), 1507 (C=C), 1465, 1451, 1443, 1241 (C-O), 1209 (C-F), 1176 (C-F), 1143 (C-F), 1032 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.60 (1H, d, *J* = 16.9, C*H*$_2$), 2.81 (1H, dd, *J* = 16.8, 4.4, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 4.58 (1H, m, C*H*NH), 4.84 (1H, s, C*H*Ph), 6.38 (1H, s, Ar*H*), 6.54 (1H, s, Ar*H*), 6.66 (1H, br d, *J* = 7.9, N*H*), 6.84 (2H, d, *J* = 8.9, Ar*H*), 7.07 (2H, d, *J* = 8.5, Ar*H*), 7.28-7.35 (5H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.6 (*C*H_2), 48.0 (*C*HNH), 55.6 (O*C*H_3), 55.9 (O*C*H_3), 56.5 (O*C*H_3), 65.8 (*C*HPh), 99.5 (Ar*C*H), 107.7 (Ar*C*CH_2), 113.9 (Ar*C*H), 115.1 (Ar*C*H), 115.8 (1C, q, *J* = 288.0, *C*F_3), 126.4 (Ar*C*H), 126.6 (Ar*C*H), 127.7 (Ar*C*H), 129.0 (Ar*C*H), 137.0 (Ar*C*N), 140.1 (Ar*C*N), 140.8 (Ar*C*CNPMP), 142.2 (Ar*C*O), 148.9 (Ar*C*O), 156.9 (1C, q, *J* = 37.1, *C*CF_3), 157.0 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 487 (28%, M^++H), 486 (100%, M^+), 471 (26%, M^+-CH_3), 372 (14%, M^+-$C_3H_5F_3O$); HRMS $C_{26}H_{25}F_3N_2O_4$ calcd. 486.1761, found 486.1746; Anal. calcd. for $C_{26}H_{25}F_3N_2O_4$: C, 64.19; H, 5.18; N, 5.76; found: C, 64.32; H, 5.17; N, 5.63%.

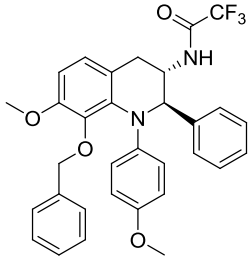
_N_-((2_R_*,3_S_*)-6,7-Dimethoxy-2-(2-methoxyphenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (272r)



272r

Prepared using general procedure N. *β*-Aminoacetamide **236r** (112 mg, 0.187 mmol) afforded crude tetrahydroquinoline **272r** as a brown oil. Purification by flash column chromatography (30% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272r** as a white solid (85 mg, 88%); mp 159-161 °C; R_f 0.44 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3416 (N-H), 3311 (N-H), 3066-2837 (C-H), 1720 (C=O), 1508 (C=C), 1489, 1464, 1452, 1441, 1284, 1240 (C-O), 1211 (C-F), 1178 (C-F), 1147 (C-F), 1031 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.64 (1H, d, *J* = 16.7, C*H*$_2$), 2.74 (1H, dd, *J* = 16.7, 4.5, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 4.80 (1H, m, C*H*NH), 5.05 (1H, s, C*H*NPMP), 6.39 (1H, s, Ar*H*), 6.53 (1H, s, Ar*H*), 6.69 (1H, br d, *J* = 8.0, N*H*), 6.84 (2H, d, *J* = 8.8, Ar*H*), 6.86 (1H, t, *J* = 7.5, Ar*H*), 6.90 (1H, d, *J* = 8.1, Ar*H*), 7.09 (2H, d, *J* = 8.5, Ar*H*), 7.25-7.29 (2H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.5 (*C*H$_2$), 45.4 (*C*HNH), 55.4 (O*C*H$_3$), 55.6 (O*C*H$_3$), 55.9 (O*C*H$_3$), 56.5 (O*C*H$_3$), 61.9 (*C*HNPMP), 99.3 (Ar*C*H), 108.1 (Ar*C*CH$_2$), 110.5 (Ar*C*H), 114.0 (Ar*C*H), 115.1 (Ar*C*H), 115.9 (1C, q, *J* = 288.3, *C*F$_3$), 120.7 (Ar*C*H), 126.6 (Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*CNPMP), 129.0 (Ar*C*H), 137.3 (Ar*C*N), 140.2 (Ar*C*N), 142.1 (Ar*C*O), 148.8 (Ar*C*O), 155.9 (Ar*C*O), 156.7 (1C, q, *J* = 36.8, *C*CF$_3$), 157.0 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.3 (3F, s, C*F*$_3$); m/z (EI) 517 (29%, M^++H), 516 (100%, M^+), 501 (17%, M^+-CH_3), 402 (15%, M^+-$C_3H_5F_3O$); HRMS $C_{27}H_{27}F_3N_2O_5$ calcd. 516.1867, found 516.1870; Anal. calcd. for $C_{27}H_{27}F_3N_2O_5$: C, 62.78; H, 5.27; N, 5.42; found: C, 63.11; H, 5.31; N, 5.38%.

_N_-((2_R_*,3_S_*)-8-(Benzyloxy)-7-methoxy-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (272s)



272s

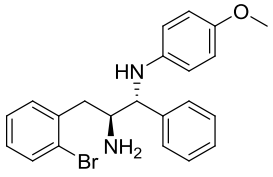
Prepared using general procedure N except with 10 mol% $Pd(PPh_3)_4$. *β*-Aminoacetamide **236s** (88 mg, 0.14 mmol) afforded crude tetrahydroquinoline **272s** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure tetrahydroquinoline **272s** as a white solid (24 mg, 31%); mp 126-128 °C; R_f 0.38 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3411 (N-H), 3302 (N-H), 3066-2853 (C-H), 1709 (C=O), 1506 (C=C), 1490, 1448, 1288, 1241 (C-O), 1206 (C-F), 1162 (C-F), 1136 (C-F), 1099, 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.76 (1H, dd, *J* = 17.2, 2.2, C*H*$_2$CHN), 2.81 (1H, dd, *J* = 17.3, 4.5, C*H*$_2$CHN), 3.74 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 4.66 (1H, m, C*H*NH), 4.71 (1H, d, *J* = 10.7, OC*H*$_2$Ph), 4.82 (1H, d, *J* = 10.6, OC*H*$_2$Ph), 5.08 (1H, d, *J* = 3.9, C*H*Ph), 6.61 (1H, d, *J* = 8.5, Ar*H*), 6.62 (1H, br m, N*H*), 6.72 (2H, dm, *J* = 8.9, Ar*H*), 6.81 (1H, d, *J* = 8.5, Ar*H*), 6.90-6.94 (4H, m, Ar*H*), 7.16-7.19 (3H, m, Ar*H*), 7.27-7.35 (5H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.7 (*C*H$_2$CHN), 48.7 (*C*HNH), 55.8 (O*C*H$_3$), 55.9 (O*C*H$_3$), 67.3 (*C*HNPMP), 73.4 (O*C*H$_2$Ph), 105.5 (Ar*C*H), 114.5 (Ar*C*H), 114.8 (Ar*C*CH$_2$CHN), 115.6 (1C, q, *J* = 288.2, *C*F$_3$), 122.2 (Ar*C*H), 125.6 (Ar*C*H), 126.0 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.0 (Ar*C*H), 129.0 (Ar*C*H), 135.8 (Ar*C*N), 137.5 (Ar*C*CH$_2$O), 138.1 (Ar*C*O), 140.4 (Ar*C*CHN), 144.7 (Ar*C*N), 153.2 (Ar*C*O), 155.7 (Ar*C*O), 156.9 (1C, q, *J* = 37.2, *C*CF$_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$); m/z (ES^+) 564 (20%, M^++H_2), 563 (65%, M^++H), 472 (100%, M^+-PhCH$_2$), 433 (55%, M^+-$C_3H_4F_3O_2$); HRMS $C_{32}H_{30}F_3N_2O_4$ calcd. 563.2158, found 563.2131.

4.4.9 Preparation of 1,2-Diamines

General Procedure O

A stirred suspension of *β*-nitroacetamide (1.00 mmol) and KOH (15.0 mmol) in EtOH (15.0 mL) and H_2O (3.0 mL) was heated to 85 °C to give a homogeneous solution. The reaction was heated until complete by TLC analysis (2-6 h) and allowed to cool to rt. H_2O (20 mL) was added and the product extracted into EtOAc (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to give crude 1,2-diamine, which was purified by passing through a short plug of silica.

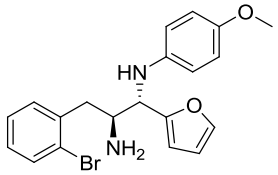
(1*R,2*S**)-3-(2-Bromophenyl)-*N*[1]-(4-methoxyphenyl)-1-phenylpropane-1,2-diamine (252a)**



252a

Prepared using general procedure O. *β*-Aminoacetamide **236a** (164 mg, 0.323 mmol) afforded crude 1,2-diamine **252a** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252a** as a pale yellow oil (124 mg, 94%); R_f 0.31 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3382 (N-H), 3059-2830 (C-H), 1511 (C=C), 1240 (C-O), 1037 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (1H, dd, *J* = 13.5, 10.5, C*H*$_2$), 3.17 (1H, dd, *J* = 13.5, 2.7, C*H*$_2$), 3.47 (1H, ddd, *J* = 10.4, 4.7, 2.9, C*H*NH_2), 3.70 (3H, s, OC*H*$_3$), 4.41 (1H, d, *J* = 4.7, C*H*Ph), 6.54 (2H, dm, *J* = 8.9, Ar*H*), 6.69 (2H, dm, *J* = 8.9, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.4, Ar*H*), 7.16 (1H, dd, *J* = 7.5, 1.4, Ar*H*), 7.23 (1H, t, *J* = 7.2, Ar*H*), 7.28 (1H, t, *J* = 7.3, Ar*H*), 7.36 (2H, t, *J* = 7.6, Ar*H*), 7.42 (2H, d, *J* = 7.4, Ar*H*), 7.55 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.7 (*C*H_2), 55.6 (*C*HNH_2), 55.8 (O*C*H_3), 63.0 (*C*HPh), 114.8 (Ar*C*H), 114.9 (Ar*C*H), 125.0 (Ar*C*CH_2), 127.5 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 131.7 (Ar*C*H), 133.2 (Ar*C*H), 138.7 (Ar*C*Br), 140.1 (Ar*C*CHN), 141.6 (Ar*C*N), 151.9 (Ar*C*O); m/z (ESI^+) 411+413 (1:1, 100%, M^++H), 290+288 (1:1, 33%, M^+-NHPMP); HRMS $C_{22}H_{24}(^{79}Br)N_2O$ calcd. 411.1064, found 411.1067; Anal. calcd. for $C_{22}H_{23}BrN_2O$: C, 64.24; H, 5.64; N, 6.81; found: C, 64.07; H, 5.81; N, 6.35%.

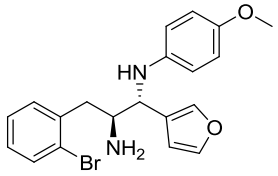
(1*S,2*S**)-3-(2-Bromophenyl)-1-(furan-2-yl)-N^1-(4-methoxyphenyl)propane-1,2-diamine (252b)**



252b

Prepared using general procedure O. *β*-Aminoacetamide **236b** (63 mg, 0.13 mmol) afforded crude 1,2-diamine **252b** as a brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252b** as a colourless oil (48 mg, 92%); R_f 0.27 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3371 (N-H), 3113-2831 (C-H), 1509 (C=C), 1470, 1440, 1234 (C-O), 1036 (C-O), 1009 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (1H, dd, *J* = 13.6, 9.5, C*H*$_2$), 3.16 (1H, dd, *J* = 13.6, 4.0, C*H*$_2$), 3.50 (1H, td, *J* = 9.1, 4.4, C*H*NH_2), 3.73 (3H, s, OC*H*$_3$), 4.52 (1H, d, *J* = 4.3, C*H*NPMP), 6.29 (1H, d, *J* = 3.2, Furyl-3-*H*), 6.35 (1H, dd, *J* = 3.1, 1.9, Furyl-4-*H*), 6.60 (2H, dm, *J* = 8.8, Ar*H*), 6.74 (2H, dm, *J* = 8.8, Ar*H*), 7.11 (1H, ddd, *J* = 7.9, 6.9, 2.2, Ar*H*), 7.24-7.28 (2H, m, Ar*H*), 7.42 (1H, m, Furyl-5-*H*), 7.57 (1H, dd, *J* = 8.2, 0.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 42.4 (*C*H_2), 54.7 (*C*HNH_2), 55.8 (O*C*H_3), 56.9 (*C*HNPMP), 108.3 (Furyl-3-*C*H), 110.5 (Furyl-4-*C*H), 114.8 (Ar*C*H), 115.1 (Ar*C*H), 125.1 (Ar*C*CH_2), 127.6 (Ar*C*H), 128.4 (Ar*C*H), 131.8 (Ar*C*H), 133.2 (Ar*C*H), 138.6 (Ar*C*Br), 141.1 (Ar*C*N), 142.1 (Furyl-5-*C*H), 152.4 (Ar*C*O), 153.8 (Furyl-2-*C*); m/z (EI) 400+402 (1:1, 4%, M^+), 202 (100%, M^+-C_8H_9BrN), 198+200 (1:1, 30%, M^+-$C_{12}H_{12}NO_2$); HRMS $C_{20}H_{21}(^{79}Br)N_2O_2$ calcd. 400.0781, found 400.0773.

(1*R,2*S**)-3-(2-Bromophenyl)-1-(furan-3-yl)-N^1-(4-methoxyphenyl)propane-1,2-diamine (252c)**

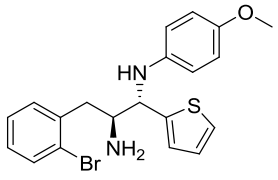


252c

Prepared using general procedure O. *β*-Aminoacetamide **236c** (54 mg, 0.11 mmol) afforded crude 1,2-diamine **252c** as a brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252c** as a colourless oil (42 mg, 96%); R_f 0.30 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3370 (N-H), 3138-2831 (C-H), 1509 (C=C), 1470, 1441, 1234 (C-O), 1023 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (1H,

dd, *J* = 13.5, 10.1, C*H*$_2$), 3.14 (1H, dd, *J* = 13.5, 3.4, C*H*$_2$), 3.44 (1H, td, *J* = 10.1, 3.8, C*H*NH$_2$), 3.73 (3H, s, OC*H*$_3$), 4.41 (1H, d, *J* = 4.3, C*H*NPMP), 6.46 (1H, m, Furyl-4-*H*), 6.61 (2H, dm, *J* = 8.9, Ar*H*), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 7.12 (1H, td, *J* = 7.6, 1.7, Ar*H*), 7.19 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.26 (1H, td, *J* = 7.4, 1.1, Ar*H*), 7.42 (1H, t, *J* = 1.7, Furyl-5-*H*), 7.45 (1H, s, Furyl-2-*H*), 7.58 (1H, dd, *J* = 8.0, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 42.3 (*C*H$_2$), 54.7 (*C*HNH$_2$), 55.3 (*C*HNPMP), 55.8 (O*C*H$_3$), 110.1 (Furyl-4-*C*H), 114.9 (Ar*C*H), 115.1 (Ar*C*H), 124.0 (Furyl-3-*C*), 125.1 (Ar*C*CH$_2$), 127.6 (Ar*C*H), 128.4 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 138.7 (Ar*C*Br), 140.8 (Furyl-2-*C*H), 141.4 (Ar*C*N), 143.4 (Furyl-5-*C*H), 152.2 (Ar*C*O); m/z (EI) 400+402 (1:1, 2%, M$^+$), 202 (100%, M$^+$-C$_8$H$_9$BrN), 198+200 (1:1, 8%, M$^+$-C$_{12}$H$_{12}$NO$_2$); HRMS $C_{20}H_{21}(^{79}Br)N_2O_2$ calcd. 400.0781, found 400.0796.

(1*S,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(thiophen-2-yl)-propane-1,2-diamine (252d)**

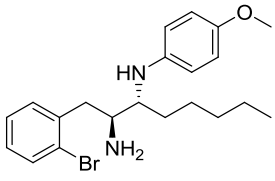


252d

Prepared using general procedure O. *β*-Aminoacetamide **236d** (165 mg, 0.321 mmol) afforded crude 1,2-diamine **252d** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252d** as a colourless oil (124 mg, 93%); R_f 0.31 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3372 (N-H), 3059-2831 (C-H), 1508 (C=C), 1469, 1439, 1233 (C-O), 1036 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (1H, dd, *J* = 13.6, 10.0, C*H*$_2$), 3.19 (1H, dd, *J* = 13.6, 3.4, C*H*$_2$), 3.49 (1H, ddd, *J* = 10.0, 4.2, 3.6, C*H*NH$_2$), 3.72 (3H, s, OC*H*$_3$), 4.70 (1H, d, *J* = 4.5, *CH*NHPMP), 6.61 (2H, dm, *J* = 8.9, Ar*H*), 6.74 (2H, dm, *J* = 8.9, Ar*H*), 7.02 (1H, dd, *J* = 5.0, 3.5, thiophenyl-4-*H*), 7.09 (1H, d, *J* = 3.0, thiophenyl-3-*H*), 7.12 (1H, td, *J* = 7.7, 1.7, Ar*H*), 7.20 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.24 (1H, dd, *J* = 5.2, 1.1. thiophenyl-5-*H*), 7.26 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.58 (1H, dd, *J* = 8.0, 1.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 42.3 (*C*H$_2$), 55.4 (*C*HNH$_2$), 55.8 (O*C*H$_3$), 59.3 (*C*HNPMP), 114.8 (Ar*C*H), 115.1 (Ar*C*H), 124.7 (thiophenyl-5-*C*H), 125.1 (Ar*C*CH$_2$), 125.9 (thiophenyl-3-*C*H), 126.9 (thiophenyl-4-*C*H), 127.6 (Ar*C*H), 128.4 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 138.6 (Ar*C*Br), 141.1 (Ar*C*N), 144.4 (thiophenyl-2-*C*), 152.3 (Ar*C*O); m/z (CI) 419+417 (100%, M+H$^+$), 294+295 (53%,

M^+-PMPNH), 219 (95%, thiophenylC^+HNHPMP); HRMS $C_{20}H_{22}(^{79}Br)N_2OS$ calcd. 417.0636, found 417.0626.

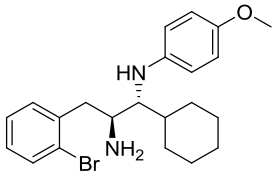
(2*S,3*R**)-1-(2-Bromophenyl)-N^3-(4-methoxyphenyl)octane-2,3-diamine (252e)**



252e

Prepared using general procedure O. *β*-Aminoacetamide **236e** (180 mg, 0.359 mmol) afforded crude 1,2-diamine **252e** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252e** as a colourless oil (140 mg, 96%); R_f 0.27 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3371 (N-H), 3056-2831 (C-H), 1508 (C=C), 1467, 1440, 1232 (C-O), 1038 (C-O), 1023 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 13.7, $(CH_2)_4CH_3$), 1.28-1.57 (7H, m, $(CH_2)_4CH_3$), 1.68-1.74 (1H, m, $(CH_2)_4CH_3$), 2.62 (1H, dd, *J* = 13.3, 9.8, CH_2Ar), 3.09 (1H, dd, *J* = 13.4, 3.9, CH_2Ar), 3.27 (1H, dt, *J* = 9.7, 3.7, $CHNH_2$), 3.35 (1H, dt, *J* = 8.8, 3.6, CHNPMP), 3.75 (3H, s, OCH_3), 6.59 (2H, dm, *J* = 8.9, ArH), 6.76 (2H, dm, *J* = 8.9, ArH), 7.11 (1H, td, *J* = 7.5, 1.7, ArH), 7.23 (1H, dd, *J* = 7.5, 1.9, ArH), 7.27 (2H, td, *J* = 7.3, 0.8, ArH), 7.57 (1H, dd, *J* = 8.0, 0.7, ArH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3 (CH_2CH_3), 22.8 (CH_2CH_3), 26.6 ($CH_2CH_2CH_3$), 30.4 ($CH_2(CH_2)_2CH_3$), 32.2 (CH_2CHNPMP), 41.2 (CH_2Ar), 53.6 ($CHNH_2$), 55.9 (OCH_3), 58.8 (CHNPMP), 114.7 (ArCH), 115.1 (ArCH), 125.0 ($ArCCH_2$), 127.6 (ArCH), 128.2 (ArCH), 131.6 (ArCH), 133.2 (ArCH), 139.2 (ArCBr), 142.6 (ArCN), 151.9 (ArCO); m/z (EI) 404+406 (2%, M^+), 206 (100%, M^+-C_8H_9BrN); HRMS $C_{21}H_{29}(^{79}Br)N_2O$ calcd. 404.1458, found 404.1464;

(1*R,2*S**)-3-(2-Bromophenyl)-1-cyclohexyl-N^1-(4-methoxyphenyl)propane-1,2-diamine (252f)**

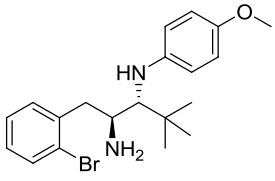


252f

Prepared using general procedure O. *β*-Aminoacetamide **236f** (65 mg, 0.13 mmol) afforded crude 1,2-diamine **252f** as a pale brown oil. Purification by passing through a short plug of

silica and eluting with EtOAc yielded pure 1,2-diamine **252f** as a colourless oil (52 mg, 98%); R_f 0.24 (80% EtOAc/Pet. ether); IR υ_{max} (neat) 3367 (N-H), 3058-2851 (C-H), 1509 (C=C), 1470, 1443, 1233 (C-O), 1041 (C-O), 1023 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.03 (1H, qd, *J* = 12.3, 3.3, Cy*H*), 1.10-1.31 (4H, m, Cy*H*), 1.65-1.77 (4H, m, Cy*H*), 1.83-1.88 (2H, m, Cy*H*), 2.50 (1H, dd, *J* = 13.2, 10.1, CH_2Ar), 3.18 (1H, dd, *J* = 12.8, 2.3, CH_2Ar), 3.23-3.27 (2H, m, C*H*NH_2 + C*H*NPMP), 3.75 (3H, s, OCH_3), 6.70 (2H, dm, *J* = 8.9, Ar*H*), 6.77 (2H, dm, *J* = 8.9, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.6, Ar*H*), 7.22 (1H, dd, *J* = 7.6, 1.7, Ar*H*), 7.26 (1H, td, *J* = 7.3, 0.9, Ar*H*), 7.56 (1H, dd, *J* = 8.0, 1.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.4 (Cy*C*H_2), 26.4 (Cy*C*H_2), 26.5 (Cy*C*H_2), 28.9 (Cy*C*H_2), 31.3 (Cy*C*H_2), 40.0 (*C*H_2Ar), 41.2 (Cy*C*HCHN), 53.1 (*C*HNH_2), 55.9 (O*C*H_3), 65.0 (*C*HNPMP), 114.2 (Ar*C*H), 115.0 (Ar*C*H), 125.0 (Ar*C*CH_2), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 131.9 (Ar*C*H), 133.2 (Ar*C*H), 139.2 (Ar*C*Br), 144.3 (Ar*C*N), 151.7 (Ar*C*O); m/z (EI) 416+418 (1:1, 7%, M^+), 218 (100%, M^+-C_8H_9BrN); HRMS $C_{22}H_{29}(^{79}Br)N_2O$ calcd. 416.1458, found 416.1441.

(2*S,3*R**)-1-(2-Bromophenyl)-*N*^{3}-(4-methoxyphenyl)-4,4-dimethylpentane-2,3-diamine (252g)**

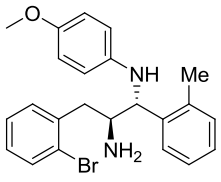


252g

Prepared using general procedure O except with 30 equiv. KOH. *β*-Aminoacetamide **236g** (58 mg, 0.12 mmol) afforded crude 1,2-diamine **252g** as a pale yellow oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252g** as a colourless oil (48 mg, 100%); R_f 0.16 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3368 (N-H), 3060-2831 (C-H), 1508 (C=C), 1469, 1440, 1230 (C-O), 1038 (C-O), 1022 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.10 (9H, s, C(CH_3)$_3$), 2.57 (1H, dd, *J* = 13.1, 10.9, CH_2), 3.20 (1H, dd, *J* = 13.1, 2.4, CH_2), 3.41-3.44 (2H, m, C*H*NH_2 + C*H*NPMP), 3.76 (3H, s, OCH_3), 6.75 (2H, dm, *J* = 9.1, Ar*H*), 6.79 (2H, dm, *J* = 9.1, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.5, Ar*H*), 7.18 (1H, dd, *J* = 7.5, 1.3, Ar*H*), 7.25 (1H, t, *J* = 7.2, Ar*H*), 7.57 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.2 (C(*C*H_3)$_3$), 36.5 (*C*(CH_3)$_3$), 40.7 (*C*H_2), 52.7 (*C*HNH_2), 55.9 (O*C*H_3), 68.7 (*C*HNPMP), 114.2 (Ar*C*H), 115.1 (Ar*C*H), 125.0 (Ar*C*CH_2), 127.5 (Ar*C*H), 128.3 (Ar*C*H), 132.3 (Ar*C*H), 133.2 (Ar*C*H), 139.2 (Ar*C*Br),

144.5 (Ar*C*N), 151.6 (Ar*C*O); m/z (EI) 390+392 (1:1, 5%, M^+), 192 (100%, M^+-C_8H_9BrN); HRMS $C_{20}H_{27}(^{79}Br)N_2O$ calcd. 390.1301, found 390.1306.

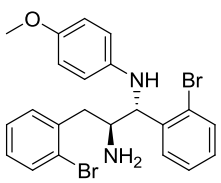
(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(*o*-tolyl)propane-1,2-diamine (252h)**



252h

Prepared using general procedure O. *β*-Aminoacetamide **236h** (67 mg, 0.13 mmol) afforded crude 1,2-diamine **252h** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252h** as a colourless oil (53 mg, 96%); R_f 0.19 (70% EtOAc/Pet. ether); IR υ_{max} (neat) 3373 (N-H), 3060-2831 (C-H), 1509 (C=C), 1233 (C-O), 1036, 1024 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.50 (1H, dd, *J* = 13.7, 11.0, C*H*$_2$), 2.53 (3H, s, ArC*H*$_3$), 3.21 (1H, dd, *J* = 13.4, 2.1, C*H*$_2$), 3.51 (1H, ddd, *J* = 10.7, 5.1, 2.4, C*H*NH_2), 3.70 (3H, s, OC*H*$_3$), 4.64 (1H, d, *J* = 5.2, C*H*NPMP), 6.50 (2H, dm, *J* = 8.8, Ar*H*), 6.70 (2H, dm, *J* = 8.8, Ar*H*), 7.09 (1H, td, *J* = 7.6, 1.5, Ar*H*), 7.17-7.21 (4H, m, Ar*H*), 7.24 (1H, td, *J* = 14.7, 0.6, Ar*H*), 7.47-7.49 (1H, m, Ar*H*), 7.53 (1H, d, *J* = 7.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.9 (ArC*C*H$_3$), 39.9 (*C*H$_2$), 54.7 (*C*HNH_2), 55.8 (O*C*H$_3$), 59.6 (*C*HNPMP), 114.9 (2 x Ar*C*H), 124.9 (Ar*C*CH$_2$), 126.4 (Ar*C*H), 127.0 (Ar*C*H), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*H), 130.9 (Ar*C*H), 131.8 (Ar*C*H), 133.3 (Ar*C*H), 136.0 (Ar*C*CH$_3$), 138.6 (Ar*C*Br), 138.9 (Ar*C*CHN), 142.0 (Ar*C*N), 152.1 (Ar*C*O); m/z (CI) 425+427 (100%, M^++H), 424+426 (28%, M^++H), 302+304 (38%, M^+-NHPMP), 226 (62%, M^+-C_8H_9BrN); HRMS $C_{23}H_{26}(^{79}Br)N_2O$ calcd. 425.1229, found 425.1210.

(1*R,2*S**)-1,3-Bis(2-bromophenyl)-*N*^{1}-(4-methoxyphenyl)propane-1,2-diamine (252i)**

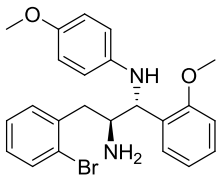


252i

Prepared using general procedure O. *β*-Aminoacetamide **236i** (74 mg, 0.13 mmol) afforded crude 1,2-diamine **252i** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252i** as a pale brown oil (63 mg,

100%); R_f 0.28 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3359 (N-H), 3057-2831 (C-H), 1510 (C=C), 1468, 1439, 1241 (C-O), 1038 (C-O), 1022 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.50 (1H, t, *J* = 12.2, C*H*$_2$), 3.20 (1H, d, *J* = 13.5, C*H*$_2$), 3.64 (1H, m, C*H*NH_2), 3.71 (3H, s, OC*H*$_3$), 4.88 (1H, d, *J* = 4.3, C*H*NPMP), 6.53 (2H, d, *J* = 8.6, Ar*H*), 6.72 (2H, d, *J* = 8.8, Ar*H*), 7.09 (1H, t, *J* = 7.5, Ar*H*), 7.15 (1H, t, *J* = 7.5, Ar*H*), 7.19 (1H, d, *J* = 7.4, Ar*H*), 7.24 (1H, t, *J* = 7.3, Ar*H*), 7.29 (1H, t, *J* = 7.4, Ar*H*), 7.53 (2H, d, *J* = 7.5, Ar*H*), 7.61 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 39.6 (*C*H_2), 54.3 (*C*HNH_2), 55.8 (O*C*H_3), 61.8 (*C*HNPMP), 114.9 (Ar*C*H), 115.0 (Ar*C*H), 124.6 (Ar*C*Br), 125.0 (Ar*C*CH_2), 127.6 (Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 129.0 (Ar*C*H), 129.4 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 133.3 (Ar*C*H), 138.7 (Ar*C*Br), 139.3 (Ar*C*CHN), 141.5 (Ar*C*N), 152.2 (Ar*C*O); m/z (CI) 489+491+493 (1:2:1, 100%, M^++H), 366+368+370 (1:2:1, 27%, M^+-NHPMP); HRMS $C_{22}H_{23}(^{79}Br)_2N_2O$ calcd. 489.0177, found 489.0170.

(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(2-methoxyphenyl)propane-1,2-diamine (252j)**

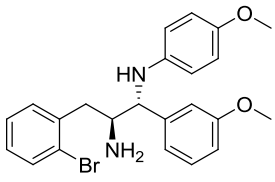


252j

Prepared using general procedure O. *β*-Aminoacetamide **236j** (159 mg, 0.300 mmol) afforded crude 1,2-diamine **252j** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252j** as a colourless oil (112 mg, 85%); R_f 0.19 (70% EtOAc/Pet. ether); IR υ_{max} (neat) 3378 (N-H), 3061-2833 (C-H), 1510 (C=C), 1488, 1464, 1439, 1234 (C-O), 1027 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (1H, dd, *J* = 13.2, 11.1, C*H*$_2$), 3.30 (1H, d, *J* = 13.6, C*H*$_2$), 3.58 (1H, ddd, *J* = 10.5, 5.3, 2.5, C*H*NH_2), 3.70 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 4.87 (1H, d, *J* = 4.6, C*H*NHPMP), 6.57 (2H, dm, *J* = 8.5, Ar*H*), 6.71 (2H, dm, *J* = 8.6, Ar*H*), 6.92-6.94 (2H, m, Ar*H*), 7.09 (1H, td, *J* = 7.5, 1.6, Ar*H*), 7.20-7.26 (3H, m, Ar*H*), 7.38 (1H, d, *J* = 7.7, Ar*H*), 7.54 (1H, d, *J* = 8.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.0 (*C*H_2), 54.6 (*C*HNH_2), 55.5 (O*C*H_3), 55.8 (O*C*H_3), 57.3 (*C*HNPMP), 110.6 (ArCH), 114.8 (ArCH), 114.8 (Ar*C*H), 120.8 (Ar*C*H), 125.1 (Ar*C*CH_2), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*CHN), 128.3 (Ar*C*H), 128.7 (Ar*C*H), 131.7 (Ar*C*H), 133.2 (Ar*C*H), 139.4 (Ar*C*Br), 141.9 (Ar*C*N), 151.9

(Ar*C*O), 157.7 (Ar*C*O); m/z (CI) 441+443 (100%, M^++H), 318+320 (8%, M^+-NHPMP), 242 (52%, M^+-C_8H_9BrN); HRMS $C_{23}H_{26}(^{79}Br)N_2O_2$ calcd. 441.1178, found 441.1163.

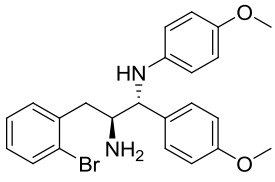
(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(3-methoxyphenyl)propane-1,2-diamine (252k)**



252k

Prepared using general procedure O. *β*-Aminoacetamide **236k** (157 mg, 0.292 mmol) afforded crude 1,2-diamine **252k** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252k** as a colourless oil (124 mg, 96%); R_f 0.14 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3382 (N-H), 3056-2832 (C-H), 1510 (C=C), 1235 (C-O), 1038 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.44 (1H, dd, *J* = 13.5, 10.5, C*H*$_2$), 3.19 (1H, dd, *J* = 13.6, 2.7, C*H*$_2$), 3.47 (1H, ddd, *J* = 10.4, 4.7, 2.9, C*H*NH_2), 3.70 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.38 (1H, d, *J* = 4.8, C*H*NHPMP), 6.56 (2H, dm, *J* = 8.9, Ar*H*), 6.71 (2H, dm, *J* = 8.9, Ar*H*), 6.83 (1H, dd, *J* = 8.1, 2.4, Ar*H*), 6.99 (1H, s, Ar*H*), 7.03 (1H, d, *J* = 7.6, Ar*H*), 7.10 (1H, td, *J* = 7.6, 1.6, Ar*H*), 7.17 (1H, dd, *J* = 7.6, 1.6, Ar*H*), 7.24 (1H, td, *J* = 7.4, 1.0, Ar*H*), 7.28 (1H, t, *J* = 7.8, Ar*H*), 7.56 (1H, dd, *J* = 7.9, 0.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.7 (*C*H_2), 55.3 (O*C*H_3), 55.6 (*C*HNH_2), 55.8 (O*C*H_3), 63.0 (*C*HNHPMP), 112.7 (ArCH), 113.7 (ArCH), 114.8 (Ar*C*H), 114.9 (Ar*C*H), 120.4 (Ar*C*H), 125.0 (Ar*C*CH_2), 127.6 (Ar*C*H), 128.4 (Ar*C*H), 129.6 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 138.7 (Ar*C*Br), 141.6 (Ar*C*N), 141.7 (Ar*C*CHN), 152.0 (Ar*C*O), 159.9 (Ar*C*O); m/z (CI) 441+443 (1:1, 100%, M^++H), 318+320 (1:1, 17%, M^+-NHPMP); HRMS $C_{23}H_{26}(^{79}Br)N_2O_2$ calcd. 441.1178, found 441.1183.

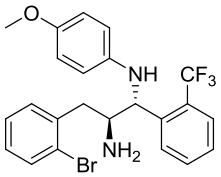
(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(4-methoxyphenyl)propane-1,2-diamine (252l)**



252l

Prepared using general procedure O. *β*-Aminoacetamide **236l** (105 mg, 0.195 mmol) afforded crude 1,2-diamine **252l** as a pale yellow oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252l** as a pale yellow oil (86 mg, 100%); R_f 0.15 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3368 (N-H), 3061-2833 (C-H), 1610, 1508 (C=C), 1469, 1440, 1239 (C-O), 1174, 1032 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (1H, dd, *J* = 13.4, 10.5, C*H*$_2$), 3.18 (1H, dd, *J* = 13.5, 2.2, C*H*$_2$), 3.44 (1H, ddd, *J* = 10.0, 4.4, 2.9, C*H*NH_2), 3.70 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.37 (1H, d, *J* = 4.6, C*H*NPMP), 6.54 (2H, d, *J* = 8.7, Ar*H*), 6.70 (2H, d, *J* = 8.7, Ar*H*), 6.90 (2H, d, *J* = 8.4, Ar*H*), 7.10 (1H, t, *J* = 7.6, Ar*H*), 7.16 (1H, d, *J* = 6.7, Ar*H*), 7.24 (1H, t, *J* = 7.4, Ar*H*), 7.34 (2H, d, *J* = 8.4, Ar*H*), 7.56 (1H, d, *J* = 8.0, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.8 (*C*H_2), 55.4 (O*C*H_3), 55.7 (*C*HNH_2), 55.8 (O*C*H_3), 62.3 (*C*HNPMP), 114.0 (Ar*C*H), 114.8 (Ar*C*H), 114.9 (Ar*C*H), 125.0 (Ar*C*CH_2), 127.5 (Ar*C*H), 128.3 (Ar*C*H), 128.9 (Ar*C*H), 131.7 (Ar*C*H), 131.9 (Ar*C*CHN), 133.2 (Ar*C*H), 138.8 (Ar*C*Br), 141.6 (Ar*C*N), 151.9 (Ar*C*O), 159.0 (Ar*C*O); m/z (EI) 440+442 (1:1, 16%, M^+), 242 (100%, M^+-C_8H_9BrN); HRMS $C_{23}H_{25}(^{79}Br)N_2O_2$ calcd. 440.1094, found 440.1088;

(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(2-(trifluoromethyl)phenyl)-propane-1,2-diamine (252m)**

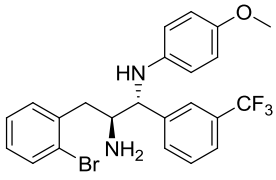


252m

Prepared using general procedure O. *β*-Aminoacetamide **236m** (100 mg, 0.174 mmol) afforded crude 1,2-diamine **252m** as a colourless oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252m** as a colourless oil (73 mg, 88%); R_f 0.34 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3351 (N-H), 3065-2833 (C-H), 1511 (C=C), 1471, 1308, 1241 (C-O), 1158 (C-F), 1117 (C-F), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.62 (1H, t, *J* = 12.2, C*H*$_2$), 3.09 (1H, d, *J* = 13.4, C*H*$_2$), 3.56 (1H, m, C*H*NH_2), 3.71 (3H, s, OC*H*$_3$), 4.81 (1H, d, *J* = 3.9, C*H*NPMP), 6.57 (2H, d, *J* = 8.8, Ar*H*), 6.72 (2H, d, *J* = 8.8, Ar*H*), 7.09 (1H, t, *J* = 7.4, Ar*H*), 7.21-7.25 (2H, m, Ar*H*), 7.41 (1H, t, *J* = 7.6, Ar*H*), 7.51 (1H, d, *J* = 7.9, Ar*H*), 7.55 (1H, t, *J* = 7.5, Ar*H*), 7.75 (1H, d, *J* = 7.9, Ar*H*), 7.88 (1H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.1 (*C*H_2), 55.3 (*C*HNH_2), 55.8 (O*C*H_3), 59.9 (*C*HNPMP), 114.8 (Ar*C*H), 115.5 (Ar*C*H), 124.8

(Ar*C*CH$_2$), 124.9 (1C, q, *J* = 274.3 *C*F$_3$), 126.7 (1C, q, *J* = 6.0, Ar*C*H), 127.6 (Ar*C*H), 127.6 (Ar*C*H), 128.3 (1C, q, *J* = 29.7, Ar*C*CF$_3$), 128.4 (Ar*C*H), 129.1 (Ar*C*H), 131.7 (Ar*C*H), 132.3 (Ar*C*H), 133.3 (Ar*C*H), 138.7 (Ar*C*Br), 140.4 (Ar*C*CHN), 141.7 (Ar*C*N), 152.5 (Ar*C*O); m/z (CI) 479+481 (1:1, 3%, M$^+$+H), 280 (5%, M$^+$-C$_8$H$_9$BrN); HRMS C$_{23}$H$_{23}$(^{79}Br)F$_3$N$_2$O calcd. 479.0946, found 479.0938.

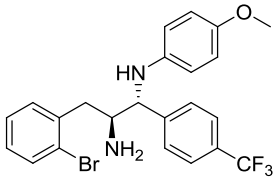
(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(3-(trifluoromethyl)phenyl)-propane-1,2-diamine (252n)**



252n

Prepared using general procedure O. *β*-Aminoacetamide **236n** (64 mg, 0.11 mmol) afforded crude 1,2-diamine **252n** as a brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252n** as a pale yellow oil (54 mg, 100%); R$_f$ 0.16 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3373 (N-H), 3056-2834 (C-H), 1510 (C=C), 1471, 1442, 1327, 1242 (C-O), 1164 (C-F), 1122 (C-F), 1072, 1038 (C-O), 1025 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.41 (1H, dd, *J* = 13.4, 10.6, C*H*$_2$), 3.09 (1H, dd, *J* = 13.5, 2.5, C*H*$_2$), 3.52 (1H, ddd, *J* = 10.4, 4.4, 3.0, C*H*NH$_2$), 3.71 (3H, s, OC*H*$_3$), 4.45 (1H, d, *J* = 4.5, C*H*NPMP), 6.52 (2H, d, *J* = 8.8, Ar*H*), 6.71 (2H, d, *J* = 8.8, Ar*H*), 7.11 (1H, td, *J* = 7.6, 1.3, Ar*H*), 7.15 (1H, dd, *J* = 7.6, 1.0, Ar*H*), 7.24 (1H, t, *J* = 7.3, Ar*H*), 7.48 (1H, t, *J* = 7.7, Ar*H*), 7.54-7.56 (2H, m, Ar*H*), 7.64 (1H, d, *J* = 7.7, Ar*H*), 7.71 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, CDCl$_3$) δ 41.1 (*C*H$_2$), 55.4 (*C*HNH$_2$), 55.8 (OC*H*$_3$), 62.9 (*C*HNPMP), 114.9 (Ar*C*H), 115.0 (Ar*C*H), 124.3 (1C, q, *J* = 272.4, *C*F$_3$), 124.5 (1C, q, *J* = 3.7, Ar*C*H), 124.6 (1C, q, *J* = 3.7, Ar*C*H), 124.9 (Ar*C*CH$_2$), 127.6 (Ar*C*H), 128.5 (Ar*C*H), 129.1 (Ar*C*H), 130.9 (1C, q, *J* = 32.1, Ar*C*CF$_3$), 131.3 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 138.3 (Ar*C*Br), 141.2 (Ar*C*N), 141.6 (Ar*C*CHN), 152.2 (Ar*C*O); m/z (CI) 479+481 (1:1, 10%, M$^+$+H), 280 (43%, M$^+$-C$_8$H$_9$BrN); HRMS C$_{23}$H$_{23}$(^{79}Br)F$_3$N$_2$O calcd. 479.0946, found 479.0937;

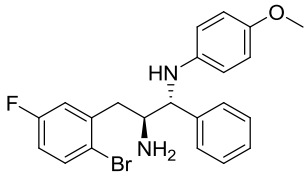
(1*R,2*S**)-3-(2-Bromophenyl)-*N*^{1}-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-propane-1,2-diamine (252o)**



252o

Prepared using general procedure O. *β*-Aminoacetamide **236o** (177 mg, 0.308 mmol) afforded crude 1,2-diamine **252o** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252o** as a colourless oil (144 mg, 98%); R_f 0.40 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3382 (N-H), 3053-2833 (C-H), 1509 (C=C), 1470, 1442, 1418, 1323, 1239 (C-O), 1162 (C-F), 1119 (C-F), 1109, 1065, 1036 (C-O), 1016 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (1H, dd, *J* = 13.4, 10.6, C*H*$_2$), 3.12 (1H, dd, *J* = 13.5, 2.7, C*H*$_2$), 3.53 (1H, ddd, *J* = 10.5, 4.4, 3.0, C*H*NH$_2$), 3.71 (3H, s, OC*H*$_3$), 4.48 (1H, d, *J* = 4.5, C*H*NPMP), 6.52 (2H, d, *J* = 8.8, Ar*H*), 6.71 (2H, d, *J* = 8.9, Ar*H*), 7.11 (1H, td, *J* = 7.6, 1.5, Ar*H*), 7.16 (1H, dd, *J* = 7.5, 1.3, Ar*H*), 7.25 (1H, td, *J* = 7.4, 0.9, Ar*H*), 7.55-7.58 (3H, m, Ar*H*), 7.63 (2H, d, *J* = 8.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.3 (*C*H$_2$), 55.4 (*C*HNH$_2$), 55.8 (O*C*H$_3$), 62.7 (*C*HNPMP), 114.9 (Ar*C*H), 114.9 (Ar*C*H), 124.3 (1C, q, *J* = 272.1, *C*F$_3$), 125.0 (Ar*C*CH$_2$), 125.6 (1C, q, *J* = 3.5, Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 129.8 (1C, q, *J* = 32.3, Ar*C*CF$_3$), 131.7 (Ar*C*H), 133.3 (Ar*C*H), 138.3 (Ar*C*Br), 141.1 (Ar*C*N), 144.6 (Ar*C*CHN), 152.2 (Ar*C*O); m/z (EI) 478+480 (1:1, 4%, M$^+$), 280 (83%, M$^+$-C$_8$H$_9$BrN), 198+200 (83%, M$^+$-C$_{15}$H$_{13}$F$_3$NO); HRMS $C_{23}H_{22}(^{79}Br)F_3N_2O$ calcd. 478.0862, found 478.0849.

(1*R,2*S**)-3-(2-Bromo-5-fluorophenyl)-*N*^{1}-(4-methoxyphenyl)-1-phenylpropane-1,2-diamine (252p)**

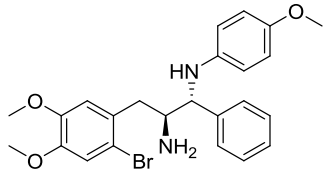


252p

Prepared using general procedure O. *β*-Aminoacetamide **236p** (106 mg, 0.202 mmol) afforded crude 1,2-diamine **252p** as a pale yellow oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252p** as a pale yellow

oil (87 mg, 100%); R_f 0.39 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3382 (N-H), 3061-2832 (C-H), 1510 (C=C), 1469, 1235 (C-O), 1030 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (1H, dd, *J* = 13.5, 10.6, CH_2), 3.14 (1H, dd, *J* = 13.6, 2.4, CH_2), 3.47 (1H, dt, *J* = 10.3, 3.5, C*H*NH_2), 3.70 (3H, s, OCH_3), 4.41 (1H, d, *J* = 4.3, C*H*NPMP), 6.55 (2H, d, *J* = 8.4, Ar*H*), 6.71 (2H, d, *J* = 8.5, Ar*H*), 6.84 (1H, td, *J* = 8.3, 3.0, Ar*H*), 6.91 (1H, dd, *J* = 9.1, 2.9, Ar*H*), 7.29 (1H, t, *J* = 7.2, Ar*H*), 7.37 (2H, t, *J* = 7.4, Ar*H*), 7.42 (2H, d, *J* = 7.5, Ar*H*), 7.50 (1H, dd, *J* = 8.8, 5.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.6 (*C*H_2), 55.6 (*C*HNH_2), 55.8 (O*C*H_3), 63.0 (*C*HNPMP), 114.9 (Ar*C*H), 115.0 (Ar*C*H), 115.5 (1C, d, *J* = 22.3, Ar*C*H), 118.5 (1C, d, *J* = 22.4, Ar*C*H), 119.0 (1C, d, *J* = 2.8, Ar*C*CH_2), 127.6 (Ar*C*H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 134.3 (1C, d, *J* = 8.1, Ar*C*H), 139.9 (Ar*C*CHN), 141.0 (1C, d, *J* = 7.3, Ar*C*Br), 141.5 (Ar*C*N), 152.0 (Ar*C*O), 161.8 (1C, d, *J* = 247.3, Ar*C*F); ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.2 (1F, m, Ar*F*); m/z (CI) 429+431 (1:1, 77%, M^++H), 428+430 (1:1, 25%, M^+), 306+308 (1:1, 28%, M^+-NHPMP), 212 (100%, M^+-C_8H_8BrFN); HRMS $C_{22}H_{23}(^{79}Br)FN_2O$ calcd. 429.0978, found 429.0965.

(1*R,2*S**)-3-(2-Bromo-4,5-dimethoxyphenyl)-*N*^{1}-(4-methoxyphenyl)-1-phenylpropane-1,2-diamine (252q)**

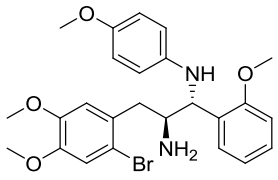


252q

Prepared using general procedure O. *β*-Aminoacetamide **236q** (139 mg, 0.245 mmol) afforded crude 1,2-diamine **252q** as a pale brown oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252q** as a colourless oil (110 mg, 95%); R_f 0.14 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3381 (N-H), 3060-2836 (C-H), 1509 (C=C), 1464, 1453, 1440, 1258 (C-O), 1240 (C-O), 1219 (C-O), 1164, 1033 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.40 (1H, dd, *J* = 13.7, 10.4, CH_2), 3.09 (1H, dd, *J* = 13.7, 2.8, CH_2), 3.45 (1H, ddd, *J* = 10.3, 4.9, 2.9, C*H*NH_2), 3.69 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.38 (1H, d, *J* = 4.9, C*H*NPMP), 6.53 (2H, dm, *J* = 8.9, Ar*H*), 6.65 (1H, s, Ar*H*), 6.69 (2H, dm, *J* = 8.9, Ar*H*), 7.01 (1H, s, Ar*H*), 7.28 (1H, t, *J* = 7.3, Ar*H*), 7.36 (2H, t, *J* = 7.6, Ar*H*), 7.43 (2H, d, *J* = 7.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.1 (*C*H_2), 55.8 (O*C*H_3), 56.1 (*C*HNH_2), 56.2 (O*C*H_3), 56.3 (O*C*H_3), 63.1 (*C*HNPMP), 114.1 (Ar*C*H), 114.7 (Ar*C*CH_2), 114.8 (Ar*C*H), 114.9 (Ar*C*H), 115.8 (Ar*C*H),

127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.6 (Ar*C*H), 130.5 (Ar*C*Br), 140.2 (Ar*C*CHN), 141.6 (Ar*C*N), 148.3 (Ar*C*O), 148.3 (Ar*C*O), 152.0 (Ar*C*O); m/z (EI) 470+472 (1:1, 5%, M^+), 258+260 (1:1, 14%, M^+-$C_{14}H_{14}NO$), 212 (100%, M^+-$C_{10}H_{13}BrNO_2$); HRMS $C_{24}H_{27}(^{79}Br)N_2O_3$ calcd. 470.1200, found 470.1204.

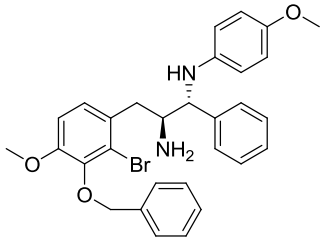
(1*R,2*S**)-3-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-methoxyphenyl)-*N*^{1}-(4-methoxyphenyl)propane-1,2-diamine (252r)**



252r

Prepared using general procedure O. *β*-Aminoacetamide **236r** (60 mg, 0.10 mmol) afforded crude 1,2-diamine **252r** as a pale yellow oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252r** as a pale yellow oil (47 mg, 94%); R_f 0.08 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3375 (N-H), 3029-2836 (C-H), 1600, 1509 (C=C), 1488, 1463, 1438, 1381, 1257 (C-O), 1235 (C-O), 1219, 1163, 1111, 1029 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (1H, dd, *J* = 13.6, 10.7, C*H*$_2$), 3.20 (1H, dd, *J* = 13.7, 1.9, C*H*$_2$), 3.55 (1H, ddd, *J* = 10.3, 5.4, 2.8, C*H*NH$_2$), 3.69 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 4.82 (1H, d, *J* = 5.2, C*H*NPMP), 6.55 (2H, dm, *J* = 8.9, Ar*H*), 6.69 (2H, dm, *J* = 9.0, Ar*H*), 6.70 (1H, s, Ar*H*), 6.91-6.93 (2H, m, Ar*H*), 7.00 (1H, s, Ar*H*), 7.24 (1H, td, *J* = 7.8, 1.6, Ar*H*), 7.36 (1H, dd, *J* = 7.7, 1.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 40.5 (*C*H$_2$), 55.0 (*C*HNH$_2$), 55.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 56.2 (O*C*H$_3$), 56.3 (O*C*H$_3$), 57.3 (*C*HNPMP), 110.6 (Ar*C*H), 114.2 (Ar*C*H), 114.7 (Ar*C*CH$_2$), 114.7 (Ar*C*H), 114.8 (Ar*C*H), 115.8 (Ar*C*H), 120.8 (Ar*C*H), 128.2 (Ar*C*CHN), 128.3 (Ar*C*H), 128.7 (Ar*C*H), 131.1 (Ar*C*Br), 141.9 (Ar*C*N), 148.2 (Ar*C*O), 148.3 (Ar*C*O), 151.9 (Ar*C*O), 157.6 (Ar*C*O); m/z (ES$^+$) 501+503 (9%, M^++H), 378+380 (80%, M^+-NHPMP), 229+231 (100%, M^+- $C_{16}H_{19}BrN_2O_2$); HRMS $C_{25}H_{30}(^{79}Br)N_2O_4$ calcd. 501.1389, found 501.1372.

(1*R,2*S**)-3-(3-(Benzyloxy)-2-bromo-4-methoxyphenyl)-*N*^{1}-(4-methoxyphenyl)-1-phenylpropane-1,2-diamine (252s)**



252s

Prepared using general procedure O. *β*-Aminoacetamide **236s** (67 mg, 0.10 mmol) afforded crude 1,2-diamine **252s** as a pale yellow oil. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure 1,2-diamine **252s** as a pale yellow oil (50 mg, 88%); R_f 0.13 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3376 (N-H), 3061-2833 (C-H), 1509 (C=C), 1483, 1463, 1453, 1439, 1293, 1272, 1239 (C-O), 1031 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (1H, dd, *J* = 13.6, 10.4, C*H*$_2$CHN), 3.15 (1H, dd, *J* = 13.7, 2.5, C*H*$_2$CHN), 3.44 (1H, ddd, *J* = 10.3, 4.6, 3.0, C*H*NH$_2$), 3.70 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 4.40 (1H, d, *J* = 4.7, C*H*NPMP), 5.02 (2H, s, OC*H*$_2$Ph), 6.54 (2H, d, *J* = 8.9, Ar*H*), 6.69 (2H, d, *J* = 8.9, Ar*H*), 6.82 (1H, d, *J* = 8.4, Ar*H*), 6.89 (1H, d, *J* = 8.5, Ar*H*), 7.28 (1H, t, *J* = 7.3, Ar*H*), 7.34-7.43 (7H, m, Ar*H*), 7.56 (2H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 41.3 (*C*H$_2$CHN), 55.6 (*C*HNH$_2$), 55.8 (O*C*H$_3$), 56.3 (O*C*H$_3$), 63.0 (*C*HNPMP), 74.6 (O*C*H$_2$Ph), 111.2 (Ar*C*H), 114.8 (2 x Ar*C*H), 121.1 (Ar*C*CH$_2$), 126.4 (Ar*C*H), 127.5 (Ar*C*H), 128.0 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (2 x Ar*C*H), 131.6 (Ar*C*Br), 137.2 (Ar*C*CH$_2$O), 140.2 (Ar*C*CHN), 141.6 (Ar*C*N), 145.6 (Ar*C*O), 151.9 (Ar*C*O), 152.6 (Ar*C*O); m/z (EI) 546+548 (1:1, 2%, M$^+$), 334+336 (1:1, 57%, M$^+$-$C_{14}H_{14}NO$), 212 (100%, M$^+$- $C_{17}H_{17}BrNO_2$); HRMS $C_{30}H_{31}(^{79}Br)N_2O_3$ calcd. 546.1513, found 546.1504.

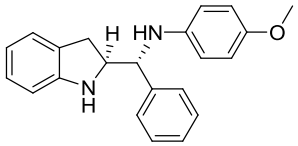
4.4.10 Preparation of Indolines

General Procedure P

A flame dried Schenk tube was charged with Pd(PPh$_3$)$_4$ (10.0 mol%), NaO^{t}Bu (1.60 mmol) and K_2CO_3 (1.60 mmol). The tube was triple evacuated/N_2 filled before the addition of a solution of 1,2-diamine (1.00 mmol) in toluene (20.0 mL). The resulting mixture was stirred while N_2 was bubbled through it, using a needle, for 15 min. The N_2 needle was removed and the reaction was heated to 100 °C for 4 h to give a dark brown mixture. The

reaction was allowed to cool to rt before being filtered through Celite®, washed with EtOAc and the solvents removed *in vacuo* to give crude indoline, which was purified by flash column chromatography.

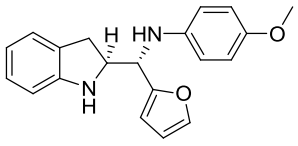
_N_-((_R_*)-((_S_*)-Indolin-2-yl)(phenyl)methyl)-4-methoxyaniline (263a)



263a

Prepared using general procedure P. 1,2-Diamine **252a** (200 mg, 0.486 mmol) afforded crude indoline **263a** as a brown solid. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263a** as a pale yellow solid (148 mg, 91%); mp 51-55 °C; R_f 0.27 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3359 (N-H), 3027-2832 (C-H), 1609, 1509 (C=C), 1483, 1466, 1454, 1237 (C-O), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.91 (1H, dd, *J* = 15.9, 8.8, C*H*$_2$), 3.18 (1H, dd, *J* = 15.9, 8.7, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 4.16 (1H, dt, *J* = 8.3, 7.1, C*H*CH_2), 4.37 (1H, d, *J* = 6.4, C*H*NPMP), 6.49 (2H, dm, *J* = 8.9, Ar*H*), 6.61 (1H, d, *J* = 7.7, Ar*H*), 6.68 (2H, d, *J* = 8.7, Ar*H*), 6.73 (1H, t, *J* = 7.4, Ar*H*), 7.05 (1H, t, *J* = 7.7, Ar*H*), 7.07 (1H, d, *J* = 7.3, Ar*H*), 7.30 (1H, t, *J* = 7.2, Ar*H*), 7.37 (2H, t, *J* = 7.4, Ar*H*), 7.42 (2H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.3 (*C*H_2), 55.8 (O*C*H_3), 62.2 (*C*HNPMP), 65.3 (*C*HCH_2), 109.2 (Ar*C*H), 114.8 (Ar*C*H), 115.4 (Ar*C*H), 119.1 (Ar*C*H), 125.0 (Ar*C*H), 127.1 (Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*CH_2), 128.9 (Ar*C*H), 141.3 (Ar*C*CHN), 141.7 (Ar*C*N), 150.5 (Ar*C*N), 152.4 (Ar*C*O); m/z (EI) 330 (3%, M^+), 213 (93%, M^+-C_8H_7N), 212 (99%, M^+-C_8H_8N), 118 (100%, M^+-$C_{14}H_{14}NO$); HRMS $C_{22}H_{22}N_2O$ calcd. 330.1727, found 330.1735; Anal. calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48; found: C, 79.79; H, 6.69; N, 8.24%.

_N_-((_S_*)-Furan-2-yl((_S_*)-indolin-2-yl)methyl)-4-methoxyaniline (263b)

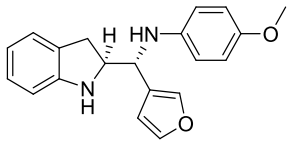


263b

Prepared using general procedure P. 1,2-Diamine **252b** (70 mg, 0.17 mmol) afforded crude indoline **263b** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263b** as an off-white semi-solid (41 mg, 75%); R_f 0.55 (30%

Et_2O/Pet. ether); IR υ_{max} (neat) 3365 (N-H), 3112-2833 (C-H), 1609, 1509 (C=C), 1484, 1465, 1234 (C-O), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.18 (2H, d, *J* = 8.0, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.24 (1H, q, *J* = 7.9, C*H*CH_2), 4.41 (1H, d, *J* = 7.6, C*H*NPMP), 6.27 (1H, d, *J* = 3.2, Furyl-3-*H*), 6.33 (1H, dd, *J* = 3.2, 1.9, Furyl-4-*H*), 6.59 (2H, dm, *J* = 8.9, Ar*H*), 6.62 (1H, d, *J* = 7.7, Ar*H*), 6.73-6.76 (3H, m, Ar*H*), 7.05 (1H, t, *J* = 7.6, Ar*H*), 7.10 (1H, d, *J* = 7.3, Ar*H*), 7.39 (1H, dd, *J* = 1.7, 0.5, Furyl-5-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 33.3 (*C*H_2), 55.8 (OCH_3), 57.1 (*C*HNPMP), 62.5 (*C*HCH_2), 107.9 (Furyl-3-*C*H), 109.4 (Ar*C*H), 110.4 (Furyl-4-*C*H), 114.8 (Ar*C*H), 115.6 (Ar*C*H), 119.0 (Ar*C*H), 125.0 (Ar*C*H), 127.5 (Ar*C*H), 128.1 (Ar*C*CH_2), 141.3 (Ar*C*N), 142.2 (Furyl-5-*C*H), 150.4 (Ar*C*N), 152.8 (Ar*C*O), 154.3 (Furyl-2-*C*); m/z (CI) 321 (5%, M^++H), 320 (2%, M^+), 202 (17%, M^+-C_8H_8N), 118 (100%, M^+-$C_{12}H_{12}NO_2$); HRMS $C_{20}H_{21}N_2O_2$ calcd. 321.1603, found 321.1607.

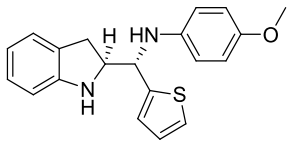
_N_-((_R_*)-Furan-3-yl((_S_*)-indolin-2-yl)methyl)-4-methoxyaniline (263c)



263c

Prepared using general procedure P. 1,2-Diamine **252c** (42 mg, 0.10 mmol) afforded crude indoline **263c** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263c** as a pale brown semi-solid (23 mg, 69%); R_f 0.30 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3359 (N-H), 3138-2832 (C-H), 1609, 1510 (C=C), 1485, 1466, 1239 (C-O), 1035 (C-O), 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.09 (1H, dd, *J* = 16.0, 8.8, C*H*$_2$), 3.13 (1H, dd, *J* = 16.0, 8.0, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.14 (1H, q, *J* = 7.9, C*H*CH_2), 4.33 (1H, d, *J* = 6.7, C*H*NPMP), 6.42 (1H, d, *J* = 0.7, Furyl-4-*H*), 6.58 (2H, dm, *J* = 8.9, Ar*H*), 6.61 (1H, d, *J* = 7.7, Ar*H*), 6.72-6.75 (3H, m, Ar*H*), 7.04 (1H, t, *J* = 7.6, Ar*H*), 7.08 (1H, d, *J* = 7.3, Ar*H*), 7.41 (1H, t, *J* = 1.5, Furyl-5-*H*), 7.42 (1H, s, Furyl-2-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.8 (*C*H_2), 55.0 (*C*HNPMP), 55.8 (OCH_3), 63.8 (*C*HCH_2), 109.1 (Furyl-4-*C*H), 109.3 (Ar*C*H), 114.8 (Ar*C*H), 115.6 (Ar*C*H), 119.1 (Ar*C*H), 125.0 (Ar*C*H), 125.7 (Furyl-3-*C*), 127.5 (Ar*C*H), 128.3 (Ar*C*CH_2), 140.4 (Furyl-2-*C*H), 141.6 (Ar*C*N), 143.7 (Furyl-5-*C*H), 150.5 (Ar*C*N), 152.6 (Ar*C*O); m/z (ESI^+) 320 (4%, M^+), 202 (100%, M^+-C_8H_8N), 118 (92%, M^+-$C_{12}H_{12}NO_2$); HRMS $C_{20}H_{20}N_2O_2$ calcd. 320.1519, found 320.1526.

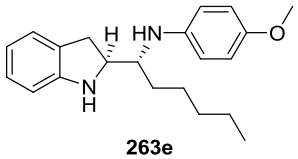
_N_-((_S_*)-((_S_*)-Indolin-2-yl)(thiophen-2-yl)methyl)-4-methoxyaniline (263d)



263d

Prepared using general procedure P. 1,2-Diamine **252d** (124 mg, 0.297 mmol) afforded crude indoline **263d** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263d** as an pale yellow solid (79 mg, 79%); mp 46-49 °C; R_f 0.33 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3360 (N-H), 3051-2832 (C-H), 1609, 1508 (C=C), 1483, 1465, 1233 (C-O), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.12 (1H, dd, *J* = 16.1, 9.0, C*H*$_2$), 3.18 (1H, dd, *J* = 16.1, 7.9, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.00 (2H, br s, N*H*), 4.18 (1H, q, *J* = 7.9, C*H*CH_2), 4.63 (1H, d, *J* = 6.8, C*H*NPMP), 6.59 (2H, dm, *J* = 9.0, Ar*H*), 6.63 (1H, d, *J* = 7.7, Ar*H*), 6.73-6.76 (3H, m, Ar*H*), 7.01 (1H, dd, *J* = 5.0, 3.5, Thiophenyl-4-*H*), 7.06 (2H, m, Ar*H* + Thiophenyl-3-yl*H*), 7.10 (1H, d, *J* = 7.3, Ar*H*), 7.24 (1H, dd, *J* = 5.0, 1.1, Thiophenyl-5-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 33.0 (*C*H_2), 55.8 (O*C*H_3), 59.1 (*C*HNPMP), 64.9 (*C*HCH_2), 109.3 (Ar*C*H), 114.8 (Ar*C*H), 115.6 (Ar*C*H), 119.1 (Ar*C*H), 124.7 (Thiophenyl-3-*C*H), 124.8 (Thiophenyl-5-*C*H), 125.0 (Ar*C*H), 127.1 (Thiophenyl-4-*C*H), 127.6 (Ar*C*H), 128.1 (Ar*C*CH_2), 141.3 (Ar*C*N), 146.3 (Thiophenyl-2-*C*), 150.3 (Ar*C*N), 152.8 (Ar*C*O); m/z (CI) 337 (30%, M^++H), 253 (5%, M^+-C_4H_3S), 218 (95%, M^+-C_8H_8N), 123 (100%, M^+- $C_{13}H_{11}NS$), 118 (19%, M^+-$C_{12}H_{12}NOS$); HRMS $C_{20}H_{21}N_2OS$ calcd. 337.1375, found 337.1386; Anal. calcd. for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33; found: C, 71.46; H, 6.02; N, 8.10%.

_N_-((_R_*)-1-((_S_*)-Indolin-2-yl)hexyl)-4-methoxyaniline (263e)

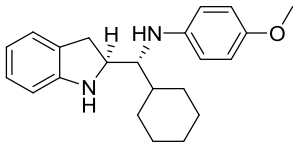


263e

Prepared using general procedure P. 1,2-Diamine **252e** (127 mg, 0.313 mmol) afforded crude indoline **263e** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263e** as an pale brown oil (70 mg, 69%); R_f 0.48 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3370 (N-H), 3052-2855 (C-H), 1609, 1509 (C=C), 1485, 1465, 1232 (C-O), 1038 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 5.7, CH_2CH_3), 1.26-1.53 (7H, m, $(CH_2)_4CH_3$), 1.66-1.71 (1H, m, C*H*$_2$CHNPMP), 2.95 (1H,

dd, *J* = 16.0, 8.5, C*H*$_2$Ar), 3.17 (1H, dd, *J* = 16.0, 9.3, C*H*$_2$Ar), 3.39 (1H, dt, *J* = 6.9, 5.0, C*H*NPMP), 3.77 (3H, s, OC*H*$_3$), 4.05 (1H, td, *J* = 8.9, 5.8, C*H*CH$_2$Ar), 6.60 (2H, d, *J* = 8.8, Ar*H*), 6.61 (1H, d, *J* = 7.9, Ar*H*), 6.72 (1H, t, *J* = 7.4, Ar*H*), 6.79 (2H, dm, *J* = 8.8, Ar*H*), 7.04 (1H, t, *J* = 7.6, Ar*H*), 7.09 (1H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.2 (CH$_2$*C*H$_3$), 22.8 (*C*H$_2$CH$_3$), 25.8 (*C*H$_2$CH$_2$CH$_3$), 31.7 (*C*H$_2$(CH$_2$)$_2$CH$_3$), 32.2 (*C*H$_2$CHNPMP), 32.9 (*C*H$_2$Ar), 55.9 (O*C*H$_3$), 58.4 (*C*HNPMP), 62.5 (*C*HCH$_2$Ar), 109.4 (Ar*C*H), 114.6 (Ar*C*H), 115.1 (Ar*C*H), 118.8 (Ar*C*H), 124.8 (Ar*C*H), 127.5 (Ar*C*H), 128.8 (Ar*C*CH$_2$), 142.5 (Ar*C*N), 151.1 (Ar*C*N), 152.0 (Ar*C*O); m/z (CI) 326 (23%, M^++H_2), 325 (100%, M^++H), 324 (6%, M^+), 118 (15%, M^+-$C_{13}H_{20}NO$); HRMS $C_{21}H_{29}N_2O$ calcd. 325.2280, found 325.2282; Anal. calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63; found: C, 77.54; H, 8.73; N, 8.65%.

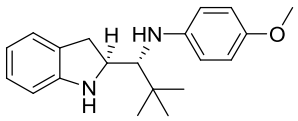
_N_-((_R_*)-Cyclohexyl((_S_*)-indolin-2-yl)methyl)-4-methoxyaniline (263f)



263f

Prepared using general procedure P. 1,2-Diamine **252f** (52 mg, 0.12 mmol) afforded crude indoline **263f** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **263f** as an off-white solid (34 mg, 82%); mp 85-88 °C; R_f 0.39 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3384 (N-H), 3051-2851 (C-H), 1609, 1509 (C=C), 1485, 1465, 1236 (C-O), 1039 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12-1.32 (5H, m, Cy*H*), 1.65-1.83 (6H, m, Cy*H*), 2.88 (1H, dd, *J* = 16.0, 8.5, C*H*$_2$Ar), 3.14 (1H, dd, *J* = 16.0, 8.9, C*H*$_2$Ar), 3.34 (1H, dd, *J* = 8.1, 3.9, C*H*NPMP), 3.75 (3H, s, OC*H*$_3$), 3.98 (1H, q, *J* = 8.6, C*H*CH$_2$Ar), 6.56 (2H, dm, *J* = 8.9, Ar*H*), 6.61 (1H, d, *J* = 7.7, Ar*H*), 6.71 (1H, t, *J* = 7.4, Ar*H*), 6.75 (2H, dm, *J* = 8.6, Ar*H*), 7.02 (1H, t, *J* = 7.7, Ar*H*), 7.05 (1H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.5 (Cy*C*H$_2$), 26.6 (Cy*C*H$_2$), 26.6 (Cy*C*H$_2$), 27.1 (Cy*C*H$_2$), 31.2 (Cy*C*H$_2$), 34.1 (*C*H$_2$Ar), 40.9 (Cy*C*HCHN), 55.9 (O*C*H$_3$), 61.9 (*C*HCH$_2$Ar), 63.7 (*C*HNPMP), 109.5 (Ar*C*H), 114.1 (Ar*C*H), 115.0 (Ar*C*H), 119.0 (Ar*C*H), 124.8 (Ar*C*H), 127.4 (Ar*C*H), 128.9 (Ar*C*CH$_2$), 143.6 (Ar*C*N), 150.7 (Ar*C*N), 151.7 (Ar*C*O); m/z (ES$^+$) 337 (19%, M^++H), 214 (100%, M^+-NHPMP); HRMS $C_{22}H_{29}N_2O$ calcd. 337.2280, found 337.2285; Anal. calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33; found: C, 78.07; H, 8.59; N, 7.75%.

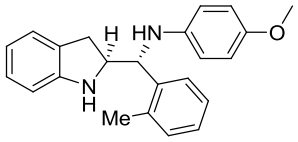
_N_-((_R_*)-1-((_S_*)-Indolin-2-yl)-2,2-dimethylpropyl)-4-methoxyaniline (263g)



263g

Prepared using general procedure P. 1,2-Diamine **252g** (48 mg, 0.12 mmol) afforded crude indoline **263g** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **263g** as a colourless oil (32 mg, 87%); R_f 0.34 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3375 (N-H), 3053-2832 (C-H), 1610, 1509 (C=C), 1486, 1466, 1232 (C-O), 1038 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.06 (9H, s, C(CH_3)$_3$), 3.00 (1H, dd, *J* = 15.8, 9.9, CH_2), 3.05 (1H, dd, *J* = 15.8, 8.9, CH_2), 3.32 (1H, d, *J* = 4.9, C*H*NPMP), 3.74 (3H, s, OCH_3), 4.23 (1H, td, *J* = 9.4, 4.8, C*H*CH_2), 6.53-6.57 (3H, m, Ar*H*), 6.69 (1H, t, *J* = 7.3, Ar*H*), 6.73 (2H, dm, *J* = 8.9, Ar*H*), 6.99 (1H, t, *J* = 7.6, Ar*H*), 7.05 (1H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.9 (C(*C*H_3)$_3$), 33.3 (*C*H_2), 36.2 (*C*(CH_3)$_3$), 55.9 (OCH_3), 62.2 (*C*HCH_2), 66.9 (*C*HNPMP), 109.6 (Ar*C*H), 114.2 (Ar*C*H), 114.9 (Ar*C*H), 118.9 (Ar*C*H), 124.5 (Ar*C*H), 127.3 (Ar*C*H), 129.0 (Ar*C*CH_2), 144.3 (Ar*C*N), 150.9 (Ar*C*N), 151.6 (Ar*C*O); m/z (ES^+) 311 (43%, M^++H), 280 (92%, M^+-OCH_3), 192 (18%, M^+-C_8H_8N), 188 (100%, M^+-NHPMP); HRMS $C_{20}H_{27}N_2O$ calcd. 311.2123, found 311.2130.

_N_-((_R_*)-((_S_*)-Indolin-2-yl)(_o_-tolyl)methyl)-4-methoxyaniline (263h)

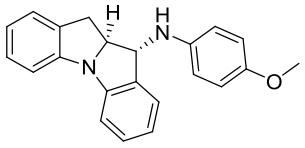


263h

Prepared using general procedure P. 1,2-Diamine **252h** (53 mg, 0.12 mmol) afforded crude indoline **263h** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263h** as an off-white solid (32 mg, 77%); mp 47-50 °C; R_f 0.34 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3355 (N-H), 3053-2832 (C-H), 1610, 1510 (C=C), 1484, 1466, 1236 (C-O), 1036 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.45 (3H, s, ArCH_3), 2.90 (1H, dd, *J* = 15.9, 8.8, CH_2), 3.24 (1H, dd, *J* = 15.9, 8.8, CH_2), 3.70 (3H, s, OCH_3), 3.75 (1H, br s, N*H*), 4.18 (1H, q, *J* = 8.0, C*H*CH_2), 4.20 (1H, br s, N*H*), 4.64 (1H, d, *J* = 6.3, C*H*NPMP), 6.43 (2H, dm, *J* = 8.9, Ar*H*), 6.60 (1H, d, *J* = 7.7, Ar*H*), 6.68 (2H, dm, *J* = 8.9, Ar*H*), 6.73 (1H, t, *J* = 7.4, Ar*H*), 7.04 (1H, t, *J* = 7.6, Ar*H*), 7.09 (1H, d, *J* =

7.3, Ar*H*), 7.19-7.22 (3H, m, Ar*H*), 7.52-7.54 (1H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.7 (ArC*C*H$_3$), 32.3 (*C*H$_2$), 55.8 (O*C*H$_3$), 58.0 (*C*HNPMP), 64.0 (*C*HCH$_2$), 109.2 (Ar*C*H), 114.8 (Ar*C*H), 115.1 (Ar*C*H), 119.0 (Ar*C*H), 125.0 (Ar*C*H), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 127.2 (Ar*C*H), 127.5 (Ar*C*H), 128.3 (Ar*C*CH$_2$), 130.8 (Ar*C*H), 135.6 (Ar*C*CH$_3$), 139.2 (Ar*C*CNPMP), 142.0 (Ar*C*N), 150.7 (Ar*C*N), 152.3 (Ar*C*O); m/z (CI) 345 (18%, M$^+$+H), 226 (17%, M$^+$-C$_8$H$_8$N), 220 (100%, M$^+$-C$_{16}$H$_{15}$NO); HRMS $C_{23}H_{25}N_2O$ calcd. 345.1967, found 345.1950.

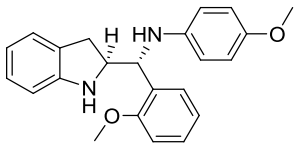
(10*R,10a*S**)-*N*-(4-Methoxyphenyl)-10a,11-dihydro-10H-indolo[1,2-a]indol-10-amine (263i)**



263i

Prepared using general procedure P except with 3.2 equiv. NaO*t*Bu and 3.2 equiv. K_2CO_3. 1,2-Diamine **252i** (49 mg, 0.10 mmol) afforded crude indoline **263i** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure indoline **263i** as a yellow solid (34 mg, 83%); mp 47-50 °C; R_f 0.17 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3367 (N-H), 3028-2832 (C-H), 1592, 1509 (C=C), 1478, 1456, 1233 (C-O), 1036 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.28 (1H, dd, *J* = 15.9, 8.6, C*H*$_2$), 3.41 (1H, dd, *J* = 15.9, 9.5, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.58 (1H, td, *J* = 9.1, 5.5, C*H*CH$_2$), 5.15 (1H, d, *J* = 5.3, C*H*NHPMP), 6.70 (2H, dm, *J* = 8.8, Ar*H*), 6.86 (2H, dm, *J* = 8.8, Ar*H*), 6.95-6.98 (2H, m, Ar*H*), 7.19-7.23 (4H, m, Ar*H*), 7.29 (1H, t, *J* = 7.8, Ar*H*), 7.31 (1H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.7 (*C*H$_2$), 55.9 (O*C*H$_3$), 63.8 (*C*HNHPMP), 73.4 (*C*HCH$_2$), 113.2 (Ar*C*H), 113.7 (Ar*C*H), 115.2 (Ar*C*H), 115.2 (Ar*C*H), 122.1 (Ar*C*H), 122.4 (Ar*C*H), 125.2 (Ar*C*H), 125.5 (Ar*C*H), 127.8 (Ar*C*H), 129.7 (Ar*C*H), 132.5 (Ar*C*CH$_2$), 133.4 (Ar*C*CNPMP), 141.3 (Ar*C*N), 148.2 (Ar*C*N), 149.2 (Ar*C*N), 152.7 (Ar*C*O); m/z (CI) 329 (39%, M$^+$+H), 328 (14%, M$^+$), 220 (42%, M$^+$-PMPH), 206 (46%, M$^+$-NHPMP); HRMS $C_{22}H_{21}N_2O$ calcd. 329.1654, found 329.1649; Anal. calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; found: C, 80.13; H, 6.13; N, 8.65%.

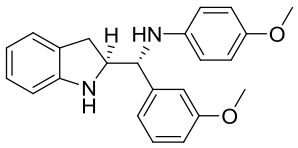
_N_-((_R_*)-((_S_*)-Indolin-2-yl)(2-methoxyphenyl)methyl)-4-methoxyaniline (263j)



263j

Prepared using general procedure P. 1,2-Diamine **252j** (105 mg, 0.238 mmol) afforded crude indoline **263j** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263j** as an off-white oily foam (57 mg, 66%); R_f 0.24 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3361 (N-H), 3030-2834 (C-H), 1601, 1509 (C=C), 1485, 1463, 1439, 1233 (C-O), 1026 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.89 (1H, dd, *J* = 15.9, 8.9, C*H*$_2$), 3.18 (1H, dd, *J* = 16.0, 8.2, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 3.89 (3H, s, OC*H*$_3$), 4.39 (1H, q, *J* = 7.9, C*H*CH_2), 4.68 (1H, s, C*H*NPMP), 6.50 (2H, dm, *J* = 8.8, Ar*H*), 6.59 (1H, d, *J* = 7.9, Ar*H*), 6.69 (2H, dm, *J* = 8.9, Ar*H*), 6.73 (1H, t, *J* = 7.0, Ar*H*), 6.93-6.95 (2H, m, Ar*H*), 7.04 (1H, t, *J* = 7.6, Ar*H*), 7.08 (1H, d, *J* = 7.3, Ar*H*), 7.25-7.28 (1H, m, Ar*H*), 7.40 (1H, d, *J* = 7.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.3 (*C*H_2), 55.5 (O*C*H_3), 55.8 (O*C*H_3), 57.7 (*C*HNPMP), 62.4 (*C*HCH_2), 109.2 (Ar*C*H), 110.8 (Ar*C*H), 114.7 (Ar*C*H), 115.3 (Ar*C*H), 118.9 (Ar*C*H), 121.0 (Ar*C*H), 125.0 (Ar*C*H), 127.4 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*CH_2), 128.6 (Ar*C*CNPMP), 128.9 (Ar*C*H), 142.2 (Ar*C*N), 150.9 (Ar*C*N), 152.2 (Ar*C*O), 157.1 (Ar*C*O); m/z (CI) 361 (30%, M^++H), 342 (31%, M^+-C_8H_8N), 123 (100%, M^+-$C_{16}H_{15}NO$), 118 (35%, M^+-$C_{15}H_{16}NO_2$); HRMS $C_{23}H_{25}N_2O_2$ calcd. 361.1911, found 361.1916.

_N_-((_R_*)-((_S_*)-Indolin-2-yl)(3-methoxyphenyl)methyl)-4-methoxyaniline (263k)

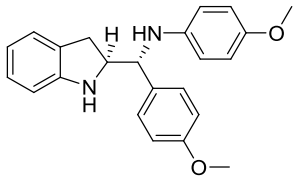


263k

Prepared using general procedure P. 1,2-Diamine **252k** (110 mg, 0.249 mmol) afforded crude indoline **263k** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263k** as an off-white solid (62 mg, 69%); mp 53-56 °C; R_f 0.29 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3360 (N-H), 3052-2833 (C-H), 1608, 1585, 1509 (C=C), 1483, 1465, 1436, 1233 (C-O), 1036 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.93 (1H, dd, *J* = 16.0, 8.8, C*H*$_2$), 3.18 (1H, dd, *J* = 16.0, 8.6, C*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 4.14 (1H, q, *J* = 7.9, C*H*CH_2), 4.20 (1H, br s, N*H*), 4.33 (1H,

d, *J* = 6.5, C*H*NPMP), 6.51 (2H, dm, *J* = 8.9, Ar*H*), 6.61 (1H, d, *J* = 7.7, Ar*H*), 6.70 (2H, dm, *J* = 8.9, Ar*H*), 6.74 (1H, t, *J* = 7.4, Ar*H*), 6.85 (1H, dd, *J* = 8.2, 2.3, Ar*H*), 7.00 (1H, s, Ar*H*), 7.03 (1H, d, *J* = 7.5, Ar*H*), 7.06 (1H, t, *J* = 7.6, Ar*H*), 7.09 (1H, d, *J* = 7.2, Ar*H*), 7.30 (1H, t, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.4 (*C*H_2), 55.3 (O*C*H_3), 55.8 (O*C*H_3), 62.2 (*C*HNPMP), 65.2 (*C*HCH$_2$), 109.2 (Ar*C*H), 112.7 (Ar*C*H), 112.8 (Ar*C*H), 114.8 (Ar*C*H), 115.4 (Ar*C*H), 119.1 (Ar*C*H), 119.4 (Ar*C*H), 125.0 (Ar*C*H), 127.5 (Ar*C*H), 128.2 (Ar*C*CH$_2$), 129.9 (Ar*C*H), 141.8 (Ar*C*N), 143.3 (Ar*C*CNPMP), 150.5 (Ar*C*N), 152.4 (Ar*C*O), 160.1 (Ar*C*O); m/z (EI) 361 (5%, M^++H), 360 (8%, M^+); HRMS $C_{23}H_{24}N_2O_2$ calcd. 360.1832, found 360.1835; Anal. calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77; found: C, 76.42; H, 6.91; N, 7.81%.

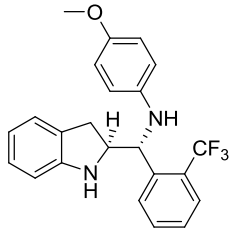
_N_-((_R_*)-((_S_*)-Indolin-2-yl)(4-methoxyphenyl)methyl)-4-methoxyaniline (263l)



263l

Prepared using general procedure P. 1,2-Diamine **252l** (46 mg, 0.10 mmol) afforded crude indoline **263l** as a brown oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) yielded pure indoline **263l** as a pale brown oil (23 mg, 64%); R_f 0.23 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3363 (N-H), 3052-2833 (C-H), 1609, 1509 (C=C), 1484, 1465, 1238 (C-O), 1174, 1034 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.93 (1H, dd, *J* = 15.9, 8.8, C*H*$_2$), 3.16 (1H, dd, *J* = 15.9, 8.6, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 4.11 (1H, q, *J* = 8.0, C*H*CH$_2$), 4.31 (1H, d, *J* = 6.5, C*H*NPMP), 6.49 (2H, d, *J* = 8.9, Ar*H*), 6.60 (1H, d, *J* = 7.7, Ar*H*), 6.69 (2H, d, *J* = 8.8, Ar*H*), 6.73 (1H, t, *J* = 7.4, Ar*H*), 6.91 (2H, d, *J* = 8.6, Ar*H*), 7.04 (1H, t, *J* = 7.6, Ar*H*), 7.08 (1H, d, *J* = 7.2, Ar*H*), 7.33 (2H, d, *J* = 8.5, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.4 (*C*H_2), 55.4 (O*C*H_3), 55.8 (O*C*H_3), 61.6 (*C*HNPMP), 65.4 (*C*HCH$_2$), 109.2 (Ar*C*H), 114.3 (Ar*C*H), 114.8 (Ar*C*H), 115.4 (Ar*C*H), 119.0 (Ar*C*H), 125.0 (Ar*C*H), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 128.3 (Ar*C*CH$_2$), 133.3 (Ar*C*CNPMP), 141.8 (Ar*C*N), 150.5 (Ar*C*N), 152.3 (Ar*C*O), 159.0 (Ar*C*O); m/z (CI) 361 (4%, M^++H), 242 (100%, M^+-C_8H_8N); HRMS $C_{23}H_{25}N_2O_2$ calcd. 361.1911, found 361.1907.

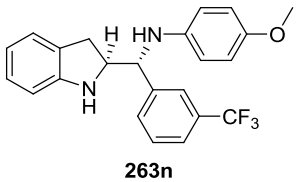
_N_-((_R_*)-((_S_*)-Indolin-2-yl)(2-(trifluoromethyl)phenyl)methyl)-4-methoxyaniline (263m)



263m

Prepared using general procedure P. 1,2-Diamine **252m** (21 mg, 44 μmol) afforded crude indoline **263m** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **263m** as a pale brown oil (13 mg, 74%); R_f 0.36 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3357 (N-H), 3031-2834 (C-H), 1609, 1511 (C=C), 1484, 1467, 1308, 1246, 1238 (C-O), 1162 (C-F), 1116 (C-F), 1035 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.60 (1H, dd, *J* = 15.8, 8.9, C*H*$_2$), 3.29 (1H, dd, *J* = 15.3, 11.1, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 4.41 (1H, td, *J* = 9.5, 3.6, C*H*CH$_2$), 4.91 (1H, d, *J* = 3.8, C*H*NPMP), 6.48 (2H, d, *J* = 8.8, Ar*H*), 6.66-6.68 (3H, m, Ar*H*), 6.74 (1H, t, *J* = 7.4, Ar*H*), 7.05-7.07 (2H, m, Ar*H*), 7.41 (1H, t, *J* = 7.5, Ar*H*), 7.54 (1H, t, *J* = 7.7, Ar*H*), 7.75 (1H, d, *J* = 7.9, Ar*H*), 7.99 (1H, d, *J* = 7.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 30.2 (*C*H$_2$), 55.8 (O*C*H$_3$), 56.9 (*C*HNPMP), 64.3 (*C*HCH$_2$), 109.6 (Ar*C*H), 114.7 (Ar*C*H), 115.8 (Ar*C*H), 119.4 (Ar*C*H), 124.8 (1C, q, *J* = 274.3, *C*F$_3$), 124.9 (Ar*C*H), 126.7 (1C, q, *J* = 6.0, Ar*C*H), 127.6 (Ar*C*H), 127.7 (Ar*C*H), 127.7 (1C, q, *J* = 29.5, Ar*C*CF$_3$), 128.2 (Ar*C*CH$_2$), 128.8 (Ar*C*H), 132.6 (Ar*C*H), 140.0 (Ar*C*N), 141.3 (Ar*C*CNPMP), 150.6 (Ar*C*N), 152.8 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -58.1 (3F, s, C*F*$_3$); m/z (CI) 399 (100%, M^++H), 398 (10%, M^+), 274 (19%, M^+-$C_7H_{10}NO$); HRMS $C_{23}H_{22}F_3N_2O$ calcd. 399.1679, found 399.1684.

_N_-((_R_*)-((_S_*)-Indolin-2-yl)(3-(trifluoromethyl)phenyl)methyl)-4-methoxyaniline (263n)

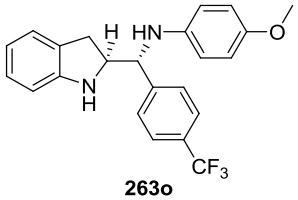


263n

Prepared using general procedure P. 1,2-Diamine **252n** (54 mg, 0.11 mmol) afforded crude indoline **263n** as a brown oil. Purification by flash column chromatography (25% Et_2O/Pet. ether) yielded pure indoline **263n** as a pale brown oil (26 mg, 59%); R_f 0.27 (25% Et_2O/Pet.

ether); IR υ_{max} (neat) 3359 (N-H), 3053-2834 (C-H), 1610, 1509 (C=C), 1484, 1467, 1436, 1326, 1237 (C-O), 1195 (C-F), 1164 (C-F), 1121 (C-F), 1071, 1036 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.85 (1H, dd, *J* = 15.9, 8.9, C*H*$_2$), 3.14 (1H, dd, *J* = 15.9, 9.2, C*H*$_2$), 3.70 (3H, s, OC*H*$_3$), 4.21 (1H, m, C*H*CH$_2$), 4.44 (1H, d, *J* = 6.0, C*H*NPMP), 6.47 (2H, d, *J* = 8.8, Ar*H*), 6.63 (1H, d, *J* = 7.7, Ar*H*), 6.70 (2H, d, *J* = 8.8, Ar*H*), 6.74 (1H, t, *J* = 7.4, Ar*H*), 7.04-7.07 (2H, m, Ar*H*), 7.49 (1H, t, *J* = 7.7, Ar*H*), 7.56 (1H, d, *J* = 7.6, Ar*H*), 7.65 (1H, d, *J* = 7.7, Ar*H*), 7.70 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.9 (*C*H$_2$), 55.8 (OCH$_3$), 62.1 (*C*HNPMP), 65.1 (*C*HCH$_2$), 109.4 (Ar*C*H), 114.8 (Ar*C*H), 115.6 (Ar*C*H), 119.4 (Ar*C*H), 123.8 (1C, q, *J* = 3.6, Ar*C*H), 124.6 (1C, q, *J* = 272.3, *C*F$_3$), 124.6 (1C, q, *J* = 3.6, Ar*C*H), 125.0 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*CH$_2$), 129.4 (Ar*C*H), 130.6 (Ar*C*H), 131.2 (1C, q, *J* = 32.2, Ar*C*CF$_3$), 141.2 (Ar*C*N), 142.5 (Ar*C*CNPMP), 150.3 (Ar*C*N), 152.7 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.8 (3F, s, C*F*$_3$); m/z (CI) 399 (52%, M^++H), 398 (10%, M^+), 280 (84%, M^+-C_8H_8N); HRMS $C_{23}H_{22}F_3N_2O$ calcd. 399.1679, found 399.1681.

_N_-((_R_*)-((_S_*)-Indolin-2-yl)(4-(trifluoromethyl)phenyl)methyl)-4-methoxyaniline (263o)

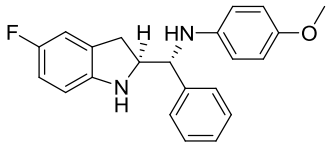


263o

Prepared using general procedure P. 1,2-Diamine **252o** (144 mg, 0.300 mmol) afforded crude indoline **263o** as a brown oil. Purification by flash column chromatography (30% Et_2O/Pet. ether) yielded pure indoline **263o** as a pale brown solid (96 mg, 80%); mp 57-60 °C; R_f 0.37 (30% Et_2O/Pet. ether); IR υ_{max} (neat) 3358 (N-H), 3054-2835 (C-H), 1610, 1511 (C=C), 1484, 1467, 1324, 1238 (C-O), 1163 (C-F), 1122 (C-F), 1066, 1036 (C-O), 1017 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.85 (1H, dd, *J* = 16.0, 8.9, C*H*$_2$), 3.16 (1H, dd, *J* = 15.9, 9.3, C*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 4.20 (1H, td, *J* = 9.0, 6.2, C*H*CH$_2$), 4.46 (1H, d, *J* = 6.0, C*H*NPMP), 6.46 (2H, dm, *J* = 8.9, Ar*H*), 6.64 (1H, d, *J* = 7.6, Ar*H*), 6.71 (2H, dm, *J* = 8.8, Ar*H*), 6.76 (1H, t, *J* = 7.4, Ar*H*), 7.06-7.09 (2H, m, Ar*H*), 7.58 (2H, d, *J* = 8.0, Ar*H*), 7.65 (2H, d, *J* = 7.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.0 (*C*H$_2$), 55.8 (OCH$_3$), 61.9 (*C*HNPMP), 65.1 (*C*HCH$_2$), 109.4 (Ar*C*H), 114.8 (Ar*C*H), 115.5 (Ar*C*H), 119.4 (Ar*C*H), 124.3 (1C, q, *J* = 272.0, *C*F$_3$), 125.0 (Ar*C*H), 125.9 (1C, q, *J* = 3.7, Ar*C*H), 127.5 (Ar*C*H),

127.7 (Ar*C*H), 128.0 (Ar*C*CH_2), 129.9 (1C, q, *J* = 32.4, Ar*C*CF_3), 141.3 (Ar*C*N), 145.6 (Ar*C*CNPMP), 150.4 (Ar*C*N), 152.7 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.8 (3F, s, C*F*$_3$); m/z (CI) 399 (13%, M^+), 280 (100%, M^+- C_8H_8N); HRMS $C_{23}H_{22}F_3N_2O$ calcd. 399.1679, found 399.1671; Anal. calcd. for $C_{23}H_{21}F_3N_2O$: C, 69.34; H, 5.31; N, 7.03; found: C, 68.95; H, 5.29; N, 6.81%.

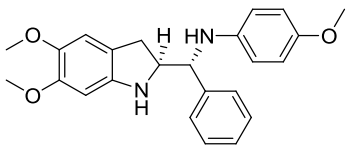
_N_-((_R_*)-((_S_*)-5-Fluoroindolin-2-yl)(phenyl)methyl)-4-methoxyaniline (263p)



263p

Prepared using general procedure P. 1,2-Diamine **252p** (46 mg, 0.11 mmol) afforded crude indoline **263p** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **263p** as a pale yellow oily solid (19 mg, 50%); R_f 0.18 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3354 (N-H), 3060-2833 (C-H), 1511 (C=C), 1488, 1451, 1236 (C-O), 1036 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.89 (1H, dd, *J* = 16.2, 8.8, C*H*$_2$), 3.15 (1H, dd, *J* = 16.2, 8.8, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 4.18 (1H, dd, *J* = 15.3, 8.6, C*H*CH_2), 4.36 (1H, d, *J* = 6.5, C*H*NHPMP), 6.48-6.51 (3H, m, Ar*H*), 6.68 (2H, dm, *J* = 8.8, Ar*H*), 6.73 (1H, td, *J* = 8.9, 2.1, Ar*H*), 6.78 (1H, d, *J* = 8.3, Ar*H*), 7.29 (1H, t, *J* = 7.2, Ar*H*), 7.36 (2H, t, *J* = 7.5, Ar*H*), 7.41 (2H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.6 (*C*H_2), 55.8 (O*C*H_3), 62.1 (*C*HPh), 65.9 (*C*HCH_2), 109.4 (1C, d, *J* = 8.3, Ar*C*H), 112.4 (1C, d, *J* = 23.9, Ar*C*H), 113.4 (1C, d, *J* = 23.2, Ar*C*H), 114.8 (Ar*C*H), 115.5 (Ar*C*H), 127.1 (Ar*C*H), 127.7 (Ar*C*H), 128.9 (Ar*C*H), 129.9 (1C, d, *J* = 8.1, Ar*C*CH_2), 141.0 (Ar*C*CHN), 141.5 (Ar*C*NPMP), 146.5 (Ar*C*N), 152.5 (Ar*C*O), 157.2 (1C, d, *J* = 235.5, Ar*C*F); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.4 (1F, m, ArF); m/z (EI) 348 (11%, M^+), 212 (100%, M^+-C_8H_7FN), 136 (92%, M^+-$C_{14}H_{14}NO$); HRMS $C_{22}H_{21}FN_2O$ calcd. 348.1632, found 348.1624.

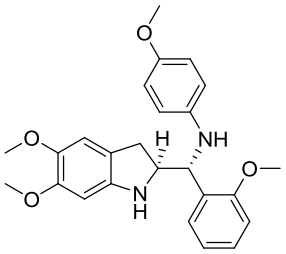
_N_-((_R_*)-((_S_*)-5,6-Dimethoxyindolin-2-yl)(phenyl)methyl)-4-methoxyaniline (263q)



263q

Prepared using general procedure P. 1,2-Diamine **252q** (109 mg, 0.231 mmol) afforded crude indoline **263q** as a brown oil. Purification by flash column chromatography (80% Et_2O/Pet. ether) yielded pure indoline **263q** as a pale yellow solid (45 mg, 50%); mp 58-61 °C; R_f 0.38 (70% Et_2O/Pet. ether); IR υ_{max} (neat) 3351 (N-H), 3061-2833 (C-H), 1509 (C=C), 1481, 1464, 1237 (C-O), 1195 (C-O), 1175, 1109, 1034 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.85 (1H, dd, *J* = 15.6, 8.9, C*H*$_2$), 3.11 (1H, dd, *J* = 15.5, 8.7, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 4.14 (1H, q, *J* = 7.9, C*H*CH_2), 4.37 (1H, d, *J* = 6.4, C*H*NPMP), 6.30 (1H, s, Ar*H*), 6.49 (2H, dm, *J* = 8.9, Ar*H*), 6.68 (2H, dm, *J* = 8.9, Ar*H*), 6.70 (1H, s, Ar*H*), 7.27-7.30 (1H, m, Ar*H*), 7.36 (2H, t, *J* = 7.6, Ar*H*), 7.42 (2H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.4 (*C*H_2), 55.8 (O*C*H_3), 56.2 (O*C*H_3), 57.1 (O*C*H_3), 62.3 (*C*HNHPMP), 66.0 (*C*HCH_2), 95.6 (Ar*C*H), 110.2 (Ar*C*H), 114.7 (Ar*C*H), 115.4 (Ar*C*H), 118.9 (Ar*C*CH_2), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 128.9 (Ar*C*H), 141.4 (Ar*C*CHN), 141.8 (Ar*C*N), 142.7 (Ar*C*O), 144.3 (Ar*C*N), 149.0 (Ar*C*O), 152.3 (Ar*C*O); m/z (EI) 390 (4%, M^+), 213 (37%, M^+-$C_{10}H_{11}NO_2$), 212 (47%, M^+-$C_{10}H_{12}NO_2$), 178 (100%, M^+-$C_{14}H_{14}NO$); HRMS $C_{24}H_{26}N_2O_3$ calcd. 390.1938, found 390.1942; Anal. calcd. for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17; found: C, 73.46; H, 6.73; N, 6.94%.

N-((*R**)-((*S**)-5,6-Dimethoxyindolin-2-yl)(2-methoxyphenyl)methyl)-4-methoxyaniline (263r)

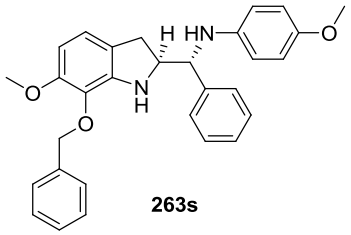


263r

Prepared using general procedure P. 1,2-Diamine **252r** (47 mg, 94 μmol) afforded crude indoline **263r** as a brown oil. Purification by flash column chromatography (70% Et_2O/Pet. ether) yielded pure indoline **263r** as an off-white solid (18 mg, 45%); mp 65-68 °C; R_f 0.52 (70% Et_2O/Pet. ether); IR υ_{max} (neat) 3357 (N-H), 2997-2834 (C-H), 1509 (C=C), 1489, 1463, 1236 (C-O), 1195, 1029 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.83 (1H, dd, *J* = 15.6, 9.0, C*H*$_2$), 3.10 (1H, dd, *J* = 15.7, 8.1, C*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 4.36 (1H, td, *J* = 8.3, 6.7, C*H*CH_2), 4.67 (1H, d, *J* = 6.1, C*H*NPMP), 6.28 (1H, s, Ar*H*), 6.49 (2H, dm, *J* = 8.9, Ar*H*), 6.68 (2H, dm, *J* = 8.9,

Ar*H*), 6.71 (1H, s, Ar*H*), 6.91-6.93 (2H, m, Ar*H*), 7.25 (1H, td, *J* = 7.8, 1.6, Ar*H*), 7.38 (1H, d, *J* = 7.4, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.5 (*C*H_2), 55.5 (O*C*H_3), 55.8 (O*C*H_3), 56.2 (O*C*H_3), 57.1 (O*C*H_3), 57.9 (*C*HNHPMP), 63.0 (*C*HCH$_2$), 95.7 (Ar*C*H), 110.3 (Ar*C*H), 110.8 (Ar*C*H), 114.7 (Ar*C*H), 115.3 (Ar*C*H), 119.3 (Ar*C*CH$_2$), 120.9 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*CHN), 128.9 (Ar*C*H), 142.2 (Ar*C*N), 142.6 (Ar*C*O), 144.7 (Ar*C*N), 148.9 (Ar*C*O), 152.2 (Ar*C*O), 157.1 (Ar*C*O); m/z (EI) 420 (10%, M^+), 243 (51%, M^+-$C_{10}H_{11}NO_2$), 242 (100%, M^+-$C_{10}H_{12}NO_2$), 178 (31%, M^+-$C_{15}H_{16}NO_2$); HRMS $C_{25}H_{28}N_2O_4$ calcd. 420.2044, found 420.2041.

_N_-((_R_*)-((_S_*)-7-(Benzyloxy)-6-methoxyindolin-2-yl)(phenyl)methyl)-4-methoxyaniline (263s)

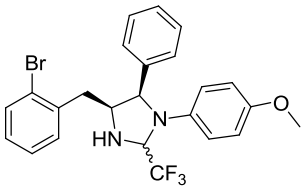


263s

Prepared using general procedure P. 1,2-Diamine **252s** (50 mg, 91 μmol) afforded crude indoline **263s** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **263s** as a pale yellow oily solid (28 mg, 66%); R_f 0.17 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3365 (N-H), 3064-2835 (C-H), 1622, 1511 (C=C), 1495, 1465, 1454, 1266, 1237 (C-O), 1090, 1038 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.79 (1H, dd, *J* = 15.4, 8.6, C*H*$_2$Ar), 3.10 (1H, dd, *J* = 15.4, 9.1, C*H*$_2$Ar), 3.70 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 3.98 (1H, m, C*H*CH$_2$Ar), 4.29 (1H, d, *J* = 6.1, C*H*NHPMP), 4.99 (2H, q, *J* = 10.4, OC*H*$_2$Ph), 6.30 (1H, d, *J* = 7.9, Ar*H*), 6.48 (2H, d, *J* = 8.6, Ar*H*), 6.69 (2H, d, *J* = 8.2, Ar*H*), 6.73 (1H, d, *J* = 7.9, Ar*H*), 7.29-7.39 (10H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 32.1 (*C*H_2), 55.8 (O*C*H_3), 56.2 (O*C*H_3), 62.2 (*C*HNHPMP), 66.3 (*C*HCH$_2$), 74.6 (OCH$_2$Ph), 102.7 (Ar*C*H), 114.7 (Ar*C*H), 115.6 (Ar*C*H), 119.7 (Ar*C*H), 122.2 (Ar*C*CH$_2$CN), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 132.1 (Ar*C*OCH$_2$), 138.1 (Ar*C*CH$_2$O), 141.1 (Ar*C*CNPMP), 141.5 (Ar*C*N), 144.8 (Ar*C*N), 152.4 (Ar*C*O), 152.5 (Ar*C*O); m/z (ES$^+$) 467 (5%, M^++H), 344 (100%, M^+-NHPMP), 253 (33%, M^+- $C_{14}H_{15}NO$); HRMS $C_{30}H_{31}N_2O_3$ calcd. 467.2315, found 467.2335.

4.4.11 Preparation of Miscellaneous Compounds

(2*R*/*S,4*S**,5*R**)-4-(2-Bromobenzyl)-1-(4-methoxyphenyl)-5-phenyl-2-(trifluoromethyl)imidazolidine (238)**

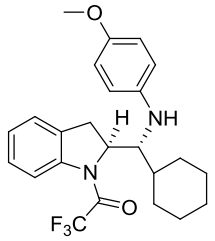


238

Formed as a by-product during the Zn/HCl reduction of *β*-nitroacetamide **232a**. To a solution of *β*-nitroacetamide **232a** (77 mg, 0.14 mmol) in EtOH (5.0 mL) at 0 °C was added 6 M aq. HCl (0.70 mL, 4.2 mmol). The colourless solution was vigorously stirred and zinc dust (549 mg, 8.40 mmol) was added in three portions over 20 min. The grey suspension was removed from the cold bath and allowed to warm to rt over 18 h. The EtOH was removed *in vacuo* and the resultant aqueous solution neutralised by the addition of sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude mixture of products as an off-white solid. Purification by flash column chromatography (20% EtOAc/Pet. ether) yielded pure imidazolidine **238** as a white solid (26 mg, 38%, 2:1 mixture of diastereomers); mp^{major} 121-123 °C; R_f^{major} 0.22 (20% EtOAc/Pet. ether); R_f^{minor} 0.31 (20% EtOAc/Pet. ether); IR υ_{max} ($CHCl_3$) 3362 (N-H), 3066-3838 (C-H), 1513 (C=C), 1284, 1247 (C-O), 1165 (C-F), 1145 (C-F) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ^{major} 2.21 (1H, dd, *J* = 13.7, 11.3, C*H*$_2$), 2.49 (1H, t, *J* = 8.2, N*H*), 2.59 (1H, dd, *J* = 13.8, 3.0, C*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 4.05-4.13 (1H, m, C*H*NH), 4.83 (1H, d, *J* = 8.0, C*H*Ph), 5.04 (1H, dt, *J* = 13.2, 4.8, C*H*CF$_3$), 6.76-6.82 (4H, m, Ar*H*), 7.07 (1H, td, *J* = 7.5, 1.7, Ar*H*), 7.17 (1H, dd, *J* = 7.5, 1.6, Ar*H*), 7.22 (1H, t, *J* = 7.4, Ar*H*), 7.34 (1H, t, *J* = 7.3, Ar*H*), 7.42 (2H, t, *J* = 7.5, Ar*H*), 7.50 (1H, d, *J* = 8.0, Ar*H*), 7.54 (2H, d, *J* = 7.6, Ar*H*); δ^{minor} 1.99 (1H, dd, *J* = 14.9, 9.7, C*H*$_2$), 2.49 (1H, dd, *J* = 9.1, 6.2, N*H*), 2.69 (1H, dd, *J* = 15.0, 4.1, C*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 4.36 (1H, m, C*H*NH), 5.13 (1H, d, *J* = 6.4, C*H*Ph), 5.40 (1H, quintet, *J* = 5.3, C*H*CF$_3$), 6.63-6.69 (4H, m, Ar*H*), 7.01 (2H, br s, Ar*H*), 7.09 (1H, td, *J* = 7.3, 2.4, Ar*H*), 7.21-7.29 (5H, m, Ar*H*), 7.53 (1H, dd, *J* = 7.6, 0.8, Ar*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ^{major} 38.6 (*C*H$_2$), 55.6 (O*C*H$_3$), 60.1 (*C*HNH), 73.3 (*C*HPh), 75.6 (1C, q, *J* = 32.7, *C*HCF$_3$), 114.4 (Ar*C*H), 117.8 (Ar*C*H), 124.4 (Ar*C*CH$_2$), 125.0 (1C, q, *J* = 283.9, *C*F$_3$), 127.3 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.7 (Ar*C*H), 132.1 (Ar*C*H), 132.7

(Ar*C*H), 138.6 (Ar*C*Br), 139.9 (Ar*C*CHN), 141.4 (Ar*C*N), 154.0 (Ar*C*O); δ^{minor} 37.8 (*C*H_2), 55.4 (O*C*H_3), 60.4 (*C*HNH), 66.5 (*C*HPh), 72.8 (1C, q, *J* = 32.7, *C*HCF_3), 114.2 (Ar*C*H), 116.9 (Ar*C*H), 124.8 (Ar*C*CH_2), 125.3 (1C, q, *J* = 288.7, *C*F_3), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 128.5 (2 x Ar*C*H), 130.4 (Ar*C*H), 132.9 (Ar*C*H), 137.5 (Ar*C*CHN), 137.8 (Ar*C*N), 138.1 (Ar*C*Br), 152.2 (Ar*C*O); ^{19}F NMR (282 MHz, $CDCl_3$) δ^{major} -75.2 (3F, s, C*F*$_3$); δ^{minor} -76.1 (3F, s, C*F*$_3$); m/z (ESI$^+$) 492+494 (1:1, 20%, M^++H_2), 491+493 (1:1, 100%, M^++H); HRMS $C_{24}H_{23}(^{79}Br)F_3N_2O$ calcd. 491.0940, found 491.0940; Anal. calcd. for $C_{24}H_{22}BrF_3N_2O$: C, 58.67; H, 4.51; N, 5.70; found: C, 58.74; H, 4.72; N, 5.35%.

1-((*S)-2-((*R**)-Cyclohexyl((4-methoxyphenyl)amino)methyl)indolin-1-yl)-2,2,2-trifluoroethanone (279)**

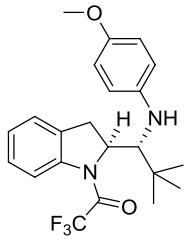


279

Formed as a by-product during the synthesis of tetrahydroquinoline **272f**. Prepared using general procedure N except with 10 mol% $Pd(PPh_3)_4$. *β*-Aminoacetamide **236f** (63 mg, 0.12 mmol) afforded crude indoline **279** as a pale brown oil. Purification by flash column chromatography (10% Et_2O/Pet. ether) yielded pure indoline **279** as a pale brown oil (10 mg, 15%); R_f 0.31 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3393 (N-H), 3035-2853 (C-H), 1677 (C=O), 1509 (C=C), 1249 (C-O), 1229, 1200 (C-F), 1179 (C-F), 1144 (C-F) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6, 90 °C) δ 1.10-1.37 (6H, m, Cy*H*), 1.57-1.66 (4H, m, Cy*H*), 1.87 (1H, d, *J* = 13.0, Cy*H*), 2.52 (1H, d, *J* = 16.1, C*H*$_2$Ar), 2.76 (1H, dd, *J* = 16.1, 9.2, C*H*$_2$Ar), 3.40 (3H, s, OC*H*$_3$), 3.69 (1H, br s, C*H*NPMP), 4.83 (1H, d, *J* = 8.6, C*H*NTFA), 6.06 (2H, d, *J* = 8.4, Ar*H*), 6.58 (2H, dm, *J* = 9.0, Ar*H*), 6.83-6.89 (3H, m, Ar*H*), 7.61 (1H, br s, Ar*H*); ^{1}H NMR$^{rotamer\ A}$ (600 MHz, C_6D_6, 25 °C, 65:35 ratio of rotamers A:B) δ 0.71-1.65 (10H, m, Cy*H*), 1.83 (1H, d, *J* = 12.5, Cy*H*), 2.28 (1H, d, *J* = 16.0, C*H*$_2$Ar), 2.57 (1H, dd, *J* = 16.0, 9.1, C*H*$_2$Ar), 3.31 (3H, s, OC*H*$_3$), 3.51 (1H, d, *J* = 8.0, C*H*NPMP), 4.69 (1H, d, *J* = 8.6, C*H*NTFA), 5.99 (2H, d, *J* = 8.4, Ar*H*), 6.61 (2H, d, *J* = 8.8, Ar*H*), 6.70-6.87 (3H, m, Ar*H*), 8.01 (1H, d, *J* = 7.2, Ar*H*); ^{1}H NMR$^{rotamer\ B}$ (600 MHz, C_6D_6, 25 °C) δ 0.71-1.65 (10H, m, Cy*H*), 1.87 (1H, br m, Cy*H*), 2.25-2.27 (1H, m, C*H*$_2$Ar), 2.46-2.51 (1H, m, C*H*$_2$Ar), 3.35 (3H, s, OC*H*$_3$), 3.92 (1H, br s, C*H*NPMP), 4.82 (1H, br s, C*H*NTFA), 6.10

(2H, br s, Ar*H*), 6.61 (2H, m, Ar*H*), 6.70-6.87 (3H, m, Ar*H*), 6.98-7.00 (1H, m, Ar*H*); ^{13}C NMR$^{rotamer\ A}$ (151 MHz, C_6D_6, 25 °C) δ 26.3 (Cy*C*H$_2$), 26.4 (Cy*C*H$_2$), 26.5 (Cy*C*H$_2$), 29.3 (*C*H$_2$Ar), 30.1 (Cy*C*H$_2$), 30.6 (Cy*C*H$_2$), 41.1 (Cy*C*H), 55.2 (O*C*H$_3$), 61.7 (*C*HNTFA), 63.7 (*C*HNPMP), 113.8 (Ar*C*H), 115.0 (Ar*C*H), 117.2 (1C, q, *J* = 288.4, *C*F$_3$), 119.4 (Ar*C*H), 123.1 (Ar*C*H), 125.5 (Ar*C*H), 127.5 (Ar*C*H), 131.9 (Ar*C*CH$_2$), 142.5 (Ar*C*N), 143.2 (Ar*C*NTFA), 152.5 (Ar*C*O), 154.0 (1C, q, *J* = 36.6, *C*CF$_3$); ^{13}C NMR$^{rotamer\ B}$ (151 MHz, C_6D_6, 25 °C) δ 26.3 (Cy*C*H$_2$), 26.4 (Cy*C*H$_2$), 26.5 (Cy*C*H$_2$), 27.7 (*C*H$_2$Ar), 30.0 (Cy*C*H$_2$), 30.2 (Cy*C*H$_2$), 40.6 (Cy*C*H), 55.3 (O*C*H$_3$), 58.9 (*C*HNPMP), 65.1 (*C*HNTFA), 113.8 (Ar*C*H), 115.0 (Ar*C*H), 115.8 (Ar*C*H), 124.7 (Ar*C*H), 125.1 (Ar*C*H), 127.3 (Ar*C*H), 133.6 (Ar*C*CH$_2$), 140.0 (Ar*C*N), 152.5 (Ar*C*O), the remaining signals could not be determined; ^{19}F NMR$^{rotamer\ A}$ (282 MHz, C_6D_6, 25 °C) δ -69.5 (3F, s, C*F*$_3$); ^{19}F NMR$^{rotamer\ B}$ (282 MHz, C_6D_6, 25 °C) δ -70.6 (3F, s, C*F*$_3$); m/z (CI) 434 (26%, M^++H_2), 433 (100%, M^++H), 432 (16%, M^+), 218 (15%, M^+-$C_{10}H_7F_3NO$); HRMS $C_{24}H_{28}F_3N_2O_2$ calcd. 433.2103, found 433.2106.

2,2,2-Trifluoro-1-((*S)-2-((*R**)-1-((4-methoxyphenyl)amino)-2,2-dimethylpropyl)indolin-1-yl)ethanone (280)**

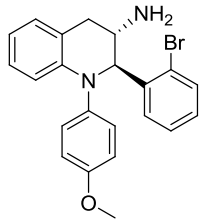


280

Formed as a by-product during the synthesis of tetrahydroquinoline **272g**. Prepared using general procedure N. *β*-Aminoacetamide **236g** (94 mg, 0.19 mmol) afforded crude indoline **280** as a dark brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) yielded pure indoline **280** as a pale brown oil (30 mg, 38%); R_f 0.38 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3410 (N-H), 2957-2833 (C-H), 1672 (C=O), 1510 (C=C), 1230, 1199 (C-F), 1170 (C-F), 1143 (C-F) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6, 90 °C) δ 0.92 (9H, s, C(C*H*$_3$)$_3$), 2.69 (1H, dd, *J* = 16.2, 1.5, C*H*$_2$), 2.81 (1H, dd, *J* = 16.2, 9.0, C*H*$_2$), 3.38 (3H, s, OC*H*$_3$), 3.77 (1H, s, C*H*NPMP), 4.99 (1H, d, *J* = 8.5, C*H*NTFA), 6.05 (2H, br s, Ar*H*), 6.53 (2H, dm, *J* = 9.0, Ar*H*), 6.76-6.85 (3H, m, Ar*H*), 7.45 (1H, br s, Ar*H*); ^{1}H NMR$^{rotamer\ A}$ (600 MHz, C_6D_6, 25 °C, 55:45 ratio of rotamers A:B) δ 0.80 (9H, s, C(C*H*$_3$)$_3$), 2.59 (1H, d, *J* = 15.7, C*H*$_2$), 2.66 (1H, dd, *J* = 16.1, 8.6, C*H*$_2$), 3.30 (3H, s, OC*H*$_3$), 3.58

(1H, s, C*H*NPMP), 4.82 (1H, d, *J* = 7.7, C*H*NTFA), 5.99 (2H, d, *J* = 6.5, Ar*H*), 6.55 (2H, d, *J* = 8.9, Ar*H*), 6.66-6.81 (3H, m, Ar*H*), 8.01 (1H, d, *J* = 6.5, Ar*H*); ^{1}H NMR$^{rotamer\ B}$ (600 MHz, C_6D_6, 25 °C) δ 0.93 (9H, s, C(CH_3)$_3$), 2.46 (1H, d, *J* = 16.2, CH_2), 2.56 (1H, dd, *J* = 16.4, 9.4, CH_2), 3.32 (3H, s, OCH_3), 3.94 (1H, s, C*H*NPMP), 4.94 (1H, d, *J* = 6.8, C*H*NTFA), 6.03 (2H, br s, Ar*H*), 6.55 (2H, d, *J* = 8.9, Ar*H*), 6.66-6.81 (3H, m, Ar*H*), 6.95 (1H, d, *J* = 7.7, Ar*H*); ^{13}C NMR$^{rotamer\ A}$ (151 MHz, C_6D_6, 25 °C) δ 27.9 (C(*C*H$_3$)$_3$), 30.9 (*C*H$_2$), 35.7 (*C*(CH$_3$)$_3$), 55.2 (O*C*H$_3$), 61.5 (*C*HNTFA), 67.5 (*C*HNPMP), 114.0 (Ar*C*H), 114.9 (Ar*C*H), 117.1 (1C, q, *J* = 288.3, *C*F$_3$), 119.5 (Ar*C*H), 122.9 (Ar*C*H), 125.6 (Ar*C*H), 127.5 (Ar*C*H), 132.0 (Ar*C*CH$_2$), 139.6 (Ar*C*NTFA), 142.9 (Ar*C*N), 152.7 (Ar*C*O), 154.1 (1C, q, *J* = 36.6, *C*F$_3$); ^{13}C NMR$^{rotamer\ B}$ (151 MHz, C_6D_6, 25 °C) δ 27.8 (C(*C*H$_3$)$_3$), 28.9 (*C*H$_2$), 35.7 (*C*(CH$_3$)$_3$), 55.3 (O*C*H$_3$), 63.5 (*C*HNPMP), 64.4 (*C*HNTFA), 114.1 (Ar*C*H), 114.9 (Ar*C*H), 115.4 (Ar*C*H), 116.9 (1C, q, *J* = 286.2, *C*F$_3$), 124.5 (Ar*C*H), 125.1 (Ar*C*H), 127.3 (Ar*C*H), 133.7 (Ar*C*CH$_2$), 139.6 (Ar*C*NTFA), 143.4 (Ar*C*N), 152.7 (Ar*C*O), 153.7 (1C, q, *J* = 39.1, C*C*F$_3$); ^{19}F NMR$^{rotamer\ A}$ (282 MHz, C_6D_6, 25 °C) δ -69.2 (3F, s, C*F*$_3$); ^{19}F NMR$^{rotamer\ B}$ (282 MHz, C_6D_6, 25 °C) δ -70.8 (3F, s, C*F*$_3$); m/z (CI) 407 (55%, M^++H), 192 (100%, M^+-$C_{10}H_7F_3NO$); HRMS $C_{22}H_{26}F_3N_2O_2$ calcd. 407.1946, found 407.1949.

(2*R,3*S**)-2-(2-Bromophenyl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinolin-3-amine (281)**

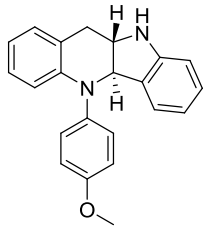


281

Prepared using general procedure O. Tetrahydroquinoline **272i** (82 mg, 0.16 mmol) afforded crude primary amine **281** as a pale brown solid. Purification by passing through a short plug of silica and eluting with EtOAc yielded pure primary amine **281** as an off-white solid (57 mg, 87%); R_f 0.19 (50% EtOAc/Pet. ether); IR υ_{max} (neat) 3363 (N-H), 3062-2836 (C-H), 1600, 1507 (C=C), 1491, 1456, 1439, 1241 (C-O), 1034 (C-O), 1021 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 (1H, d, *J* = 16.3, CH_2), 2.86 (1H, dd, *J* = 16.3, 3.8, CH_2), 3.57 (1H, d, *J* = 2.3, C*H*NH$_2$), 3.79 (3H, s, OCH_3), 4.92 (1H, s, C*H*NPMP), 6.55 (1H, d, *J* = 8.3, Ar*H*), 6.72 (1H, t, *J* = 7.3, Ar*H*), 6.86 (2H, d, *J* = 8.8, Ar*H*), 7.01 (1H, t, *J* = 7.6, Ar*H*), 7.07 (1H, d, *J* = 7.3, Ar*H*), 7.11 (1H, td, *J* = 7.4, 1.3, Ar*H*), 7.13 (2H, d, *J* = 8.5, Ar*H*), 7.25 (1H,

t, *J* = 7.4, Ar*H*), 7.45 (1H, dd, *J* = 7.8, 1.0, Ar*H*), 7.51 (1H, d, *J* = 7.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.5 (*C*H_2), 46.7 (*C*HNH_2), 55.5 (O*C*H_3), 71.2 (*C*HNPMP), 112.8 (Ar*C*H), 115.1 (Ar*C*H), 117.6 (Ar*C*H), 117.7 (Ar*C*CH_2), 122.4 (Ar*C*CHPMP), 127.4 (Ar*C*H), 127.7 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 130.9 (Ar*C*H), 133.2 (Ar*C*H), 139.5 (Ar*C*N), 141.7 (Ar*C*Br), 144.4 (Ar*C*N), 157.5 (Ar*C*O); m/z (EI) 409+411 (1:1, 25%, M^++H), 408+410 (1:1, 100%, M^+); HRMS $C_{22}H_{21}(^{79}Br)N_2O$ calcd. 408.0832, found 408.0836.

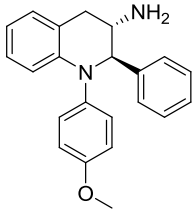
(5a*R,10a*S**)-5-(4-Methoxyphenyl)-5a,10,10a,11-tetrahydro-5H-indolo[3,2-b]quinoline (282)**



282

Prepared using general procedure P. Primary amine **281** (52 mg, 0.13 mmol) afforded crude tetrahydroindoloquinoline **282** as a black oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) yielded pure tetrahydroindoloquinoline **282** as an off-white solid (17 mg, 40%); mp 175-180 °C (deg.); R_f 0.49 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3351 (N-H), 3052-2774 (C-H), 1607, 1508 (C=C), 1485, 1461, 1453, 1324, 1241 (C-O), 1220, 1033 (C-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.21 (1H, dd, *J* = 14.8, 4.9, C*H*$_2$), 3.44 (1H, t, *J* = 13.4, C*H*$_2$), 3.92 (3H, s, OC*H*$_3$), 4.05 (1H, td, *J* = 11.7, 4.9, C*H*NH), 4.66 (1H, d, *J* = 11.2, C*H*NPMP), 5.93 (1H, d, *J* = 7.6, Ar*H*), 6.36 (1H, d, *J* = 8.3, Ar*H*), 6.55 (1H, t, *J* = 7.5, Ar*H*), 6.77 (1H, t, *J* = 7.3, Ar*H*), 6.79 (1H, d, *J* = 8.5, Ar*H*), 6.98 (1H, t, *J* = 7.7, Ar*H*), 7.04-7.06 (3H, m, Ar*H*), 7.15 (1H, d, *J* = 7.4, Ar*H*), 7.30 (2H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.5 (*C*H_2), 55.6 (O*C*H_3), 63.7 (*C*HNH), 66.3 (*C*HNPMP), 111.1 (Ar*C*H), 115.1 (Ar*C*H), 115.8 (Ar*C*H), 118.7 (Ar*C*H), 119.6 (Ar*C*H), 121.3 (Ar*C*CH_2), 124.7 (Ar*C*H), 127.2 (Ar*C*H), 128.0 (Ar*C*H), 129.0 (Ar*C*CHNPMP), 130.7 (Ar*C*H), 131.3 (Ar*C*H), 138.6 (Ar*C*N), 148.4 (Ar*C*N), 150.8 (Ar*C*N), 158.7 (Ar*C*O); m/z (EI) 329 (18%, M^++H), 328 (100%, M^+), 327 (34%, M^+-H); HRMS $C_{22}H_{20}N_2O$ calcd. 328.1570, found 328.1568.

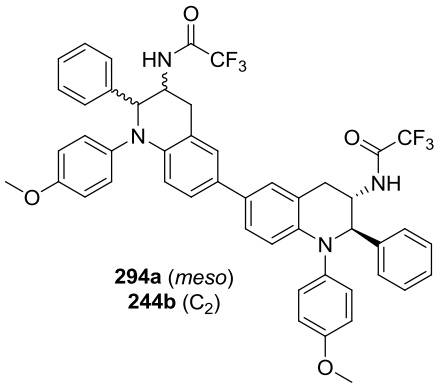
(2*R,3*S**)-1-(4-Methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-amine (265)**



265

To a colourless solution of tetrahydroquinoline **272a** (155 mg, 0.363 mmol) in *i*PrOH (25 mL) and H_2O (2.5 mL) at rt was added $NaBH_4$ (137 mg, 3.63 mmol). The mixture was stirred at rt for 5 h before removal of the *i*PrOH *in vacuo*. The residue was diluted with H_2O (15 mL) and the product extracted into CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$) and the concentrated *in vacuo* to yield crude tetrahydroquinoline **265** as a pale yellow solid. Purification by flash column chromatography (5% Et_3N/EtOAc) gave pure **265** as a white solid (97 mg, 82%); mp 153-155 °C; R_f 0.33 (5% Et_3N/EtOAc); IR υ_{max} (neat) 3362 (N-H), 3060-2835 (C-H), 1599, 1506 (C=C), 1489, 1454, 1237 (C-O), 1031 (C-O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.60 (1H, dd, *J* = 16.2, 3.0, C*H*$_2$), 2.90 (1H, dd, *J* = 16.2, 4.2, C*H*$_2$), 3.45 (1H, q, *J* = 3.9, C*H*NH_2), 3.78 (3H, s, OC*H*$_3$), 4.57 (1H, d, *J* = 2.6, C*H*Ph), 6.61 (1H, d, *J* = 8.3, Ar*H*), 6.71 (1H, t, *J* = 7.3, Ar*H*), 6.84 (2H, dm, *J* = 9.0, Ar*H*), 7.01 (1H, t, *J* = 7.8, Ar*H*), 7.06 (1H, d, *J* = 7.5, Ar*H*), 7.14 (2H, dm, *J* = 8.8, Ar*H*), 7.22-7.31 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.9 (*C*H_2), 49.2 (C*H*NH_2), 55.1 (O*C*H_3), 71.1 (*C*HPh), 112.9 (Ar*C*H), 114.5 (Ar*C*H), 117.0 (Ar*C*H), 118.1 (Ar*C*CH_2), 126.3 (Ar*C*H), 126.8 (2 x Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 130.4 (Ar*C*H), 139.6 (Ar*C*N), 142.7 (Ar*C*CHN), 144.0 (Ar*C*N), 156.9 (Ar*C*O); m/z (EI) 330 (100%, M^+), 239 (60%, M^+-NPh), 224 (25%, M^+-PMP); HRMS $C_{22}H_{22}N_2O$ calcd. 330.1727, found 330.1730.

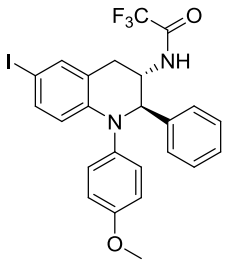
_N_,_N_'-((2_R_*,2'_R_/_S_*,3_S_*,3'_S_/_R_*)-1,1'-Bis(4-methoxyphenyl)-2,2'-diphenyl-1,1',2,2',3,3',4,4'-octahydro-[6,6'-biquinoline]-3,3'-diyl)bis(2,2,2-trifluoroacetamide) (294a/b)



To an orange solution of CAN (297 mg, 0.539 mmol) in H_2O (2 mL) at 0 °C was added dropwise a solution of tetrahydroquinoline **272a** (115 mg, 0.270 mmol) in MeCN (10 mL) to give a black solution. The reaction was stirred at 0 °C for 1 h before being removed from the ice bath and allowed to warm to rt over 1 h. The reaction was diluted with H_2O (10 mL) and the product extracted in to CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude dimerised product **294** as a brown oil. Purification by flash column chromatography (20% EtOAc/Pet. ether) gave pure **294** as a brown oil (53 mg, 46%) consisting of a mixture of *meso* (**294a**) and C_2 symmetric (**294b**) products in approximately 1:1 ratio (determined by ^{13}C NMR); R_f 0.40 (20% EtOAc/Pet. ether); IR υ_{max} (neat) 3415 (N-H), 3296 (N-H), 3061-2838 (C-H), 1712 (C=O), 1507 (C=C), 1486, 1240 (C-O), 1204 (C-F), 1160 (C-F), 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.75 (2H, br d, *J* = 16.6, C*H*$_2$), 3.00 (2H, br d, *J* = 15.6, C*H*$_2$), 3.80 (6H, s, OC*H*$_3$), 4.60 (2H, m, C*H*NTFA), 4.90 (2H, br s, C*H*Ph), 6.69 (2H, br d, *J* = 7.5, N*H*), 6.75 (2H, br d, *J* = 8.0, Ar*H*), 6.87 (4H, br d, *J* = 8.3, Ar*H*), 7.09 (4H, br d, *J* = 8.1, Ar*H*), 7.24-7.38 (14H, m, Ar*H*) (the presence of the *meso* and C_2 symmetric products could not be determined by ^1H NMR); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.5 (*C*H$_2$), 47.4 (*C*HNTFA), 55.1 (O*C*H$_3$), 66.0 (*C*HPh), 114.0 (Ar*C*H), 114.0 (Ar*C*H), 114.9 (Ar*C*H), 115.4 (1C, q, *J* = 287.9, *C*F$_3$), 115.9 (Ar*C*CH$_2$), 116.0 (Ar*C*CH$_2$), 125.5 (Ar*C*H), 126.1 (Ar*C*H), 126.7 (Ar*C*Ar), 127.3 (Ar*C*Ar), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*N), 128.6 (Ar*C*H), 130.1 (Ar*C*N), 138.7 (Ar*C*N), 138.8 (Ar*C*N), 140.5 (Ar*C*CHN), 142.1 (Ar*C*CHN), 156.6 (1C, q, *J* = 37.2, *C*CF$_3$), 157.3 (Ar*C*O) (no further signals could be determined due to overlying peaks for the *meso* and C_2 symmetric products); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.2 (6F, s, 2 x C*F*$_3$); m/z (ES^+) 849

(15%, M^+-H), 848 (45%, M^+-H_2), 847 (100%, M^+-H_3), 753 (5%, M^+-TFA), 752 (20%, M^+-TFAH), 751 (35%, M^+-$TFAH_2$); HRMS $C_{48}H_{37}F_6N_4O_4$ calcd. 847.2719, found 847.2713.

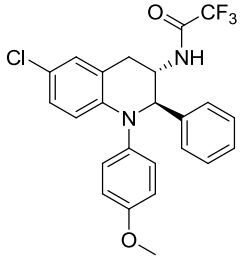
2,2,2-Trifluoro-*N*-((2*R,3*S**)-6-iodo-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (304)**



304

To a colourless solution of tetrahydroquinoline **272a** (39 mg, 91 μmol) in MeCN (8 mL) and H_2O (2 mL) at rt was added H_5IO_6 (21 mg, 91 μmol) and H_2SO_4 (1 M in H_2O, 91μL, 91 μmol). The reaction was heated to 90 °C for 5 h, giving a pale brown solution, before being allowed to cool to rt. The reaction was diluted with H_2O (10 mL) and the product extracted in to CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude tetrahydroquinoline **304** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) gave pure **304** as a white solid (34 mg, 68%); mp 154-156 °C; R_f 0.49 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3417, 3294 (N-H), 3063-2837 (C-H), 1709 (C=O), 1508 (C=C), 1485, 1241 (C-O), 1207 (C-F), 1176 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.65 (1H, d, *J* = 17.2, C*H*$_2$), 2.91 (1H, dd, *J* = 17.1, 4.4, C*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 4.51-4.54 (1H, m, C*H*NH), 4.85 (1H, s, C*H*Ph), 6.43 (1H, d, *J* = 8.8, Ar*H*), 6.56 (1H, br d, *J* = 7.6, N*H*), 6.85 (2H, d, *J* = 8.6, Ar*H*), 7.02 (2H, d, *J* = 9.0, Ar*H*), 7.29-7.36 (7H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.4 (*C*H_2), 47.4 (*C*HNH), 55.6 (O*C*H_3), 66.3 (*C*HPh), 115.4 (Ar*C*H), 115.7 (1C, q, *J* = 288.2, *C*F_3), 116.0 (Ar*C*H), 118.6 (Ar*C*CH_2), 126.3 (Ar*C*H), 128.0 (Ar*C*H), 128.1 (Ar*C*H), 129.1 (Ar*C*H), 136.8 (Ar*C*H), 138.4 (Ar*C*N), 138.9 (Ar*C*H), 140.6 (Ar*C*CHN), 143.7 (Ar*C*N), 156.8 (1C, q, *J* = 37.4, *C*CF_3), 158.0 (Ar*C*O), the remaining signal (Ar*C*I) could not be determined; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.1 (3F, s, C*F*$_3$); m/z (EI) 552 (23%, M^+); HRMS $C_{24}H_{20}F_3IN_2O_2$ calcd. 552.0516, found 552.0530; Anal. calcd. for $C_{24}H_{20}F_3IN_2O_2$: C, 52.19; H, 3.65; N, 5.07; found: C, 52.12; H, 3.76; N, 4.97%.

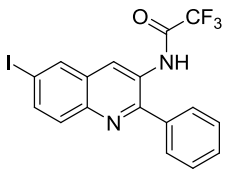
_N_-((2_R_*,3_S_*)-6-Chloro-1-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-2,2,2-trifluoroacetamide (305)



305

To a colourless solution of tetrahydroquinoline **272a** (45 mg, 0.11 mol) in MeCN (8 mL) and H_2O (2 mL) at rt was added TCCA (12 mg, 53 μmol) and H_2SO_4 (1 M in H_2O, 0.11 mL, 0.11 mmol). The dark brown mixture was heated to 90 °C for 5 h before being allowed to cool to rt. The reaction was diluted with H_2O (10 mL) and the product extracted in to CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude tetrahydroquinoline **305** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) gave pure **305** as a colourless oil (6.0 mg, 12%); R_f 0.27 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3289 (N-H), 3065-2849 (C-H), 1699 (C=O), 1507 (C=C), 1452, 1242 (C-O), 1204 (C-F), 1180 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.84 (1H, dd, *J* = 17.5, 5.3, C*H*$_2$), 2.92 (1H, dd, *J* = 17.5, 2.3, C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 4.82-4.85 (1H, m, C*H*NH), 5.20 (1H, d, *J* = 3.3, C*H*Ph), 6.67 (1H, br d, *J* = 6.5, N*H*), 6.80 (2H, d, *J* = 9.1, Ar*H*), 6.87 (2H, d, *J* = 8.6, Ar*H*), 6.93 (1H, t, *J* = 7.7, Ar*H*), 6.97 (1H, dt, *J* = 7.4, 0.6, Ar*H*), 7.27-7.37 (6H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.2 (*C*H_2), 49.3 (*C*HNH), 55.6 (O*C*H_3), 66.9 (*C*HPh), 115.0 (Ar*C*H), 115.5 (1C, q, *J* = 287.9, *C*F_3), 121.7 (Ar*C*H), 123.1 (Ar*C*H), 125.9 (Ar*C*H), 126.2 (Ar*C*CH_2), 127.2 (Ar*C*Cl), 127.8 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*H), 130.2 (Ar*C*H), 138.5 (Ar*C*N), 139.3 (Ar*C*CHN), 144.3 (Ar*C*N), 155.6 (Ar*C*O), 156.8 (1C, q, *J* = 37.4, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.5 (3F, s, C*F*$_3$); m/z (EI) 461 (134%, M^++H), 460 (100%, M^+); HRMS $C_{24}H_{20}ClF_3N_2O_2$ calcd. 460.1160, found 460.1163.

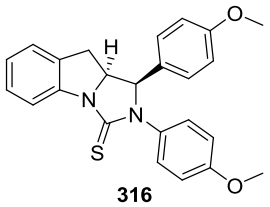
2,2,2-Trifluoro-_N_-(6-iodo-2-phenylquinolin-3-yl)acetamide (307)



307

To a colourless solution of tetrahydroquinoline **272a** (41 mg, 96 μmol) in MeCN (5.0 mL) and H_2O (2.5 mL) at rt was added H_5IO_6 (44 mg, 0.19 mmol). The reaction was heated to 80 °C for 18 h to give a dark brown solution. After being allowed to cool to rt the reaction was diluted with H_2O (10 mL) and the product extracted in to CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude quinoline **307** as a brown oil. Purification by flash column chromatography (15% EtOAc/Pet. ether) gave pure **307** as a pale yellow solid (18 mg, 53%); mp 150-152 °C; R_f 0.45 (15% EtOAc/Pet. ether); IR υ_{max} (neat) 3392 (N-H), 3059-2851 (C-H), 1732 (C=O), 1543 (C=C), 1472 (C=N), 1217 (C-F), 1181 (C-F) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58-7.66 (5H, m, Ph*H*), 7.84 (1H, d, *J* = 8.8, quinolinyl-8-*H*), 7.97 (1H, dd, *J* = 8.8, 1.8, quinolinyl-7-*H*), 8.31 (1H, d, *J* = 1.7, quinolinyl-5-*H*), 8.34 (1H, br s, N*H*), 9.08 (1H, s, quinolinyl-4-*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 93.6 (quinolinyl-6-*C*I), 115.4 (1C, q, *J* = 288.1, *C*F_3), 125.0 (quinolinyl-4-*C*H), 127.5 (quinolinyl*C*), 128.8 (Ph*C*H), 129.1 (quinolinyl-2-*C*Ph), 129.9 (Ph*C*H), 130.4 (Ph*C*H), 131.0 (quinolinyl-8-*C*H), 135.8 (Ph*C*), 136.5 (quinolinyl-5-*C*H), 138.6 (quinolinyl-7-*C*H), 144.5 (quinolinyl-*C*), 152.1 (quinolinyl-3-*C*NTFA), 155.0 (1C, q, *J* = 37.9, *C*CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (3F, s, C*F*$_3$); m/z (EI) 442 (100%, M^+), 373 (85%, M^+-CF_3), 246 (25%, M^+-(I+CF_3)); HRMS $C_{17}H_{10}F_3IN_2O$ calcd. 441.9785, found 441.9792.

(1*R,9a*S**)-1,2-Bis(4-methoxyphenyl)-9,9a-dihydro-1H-imidazo[1,5-a]indole-3(2H)-thione (316)**

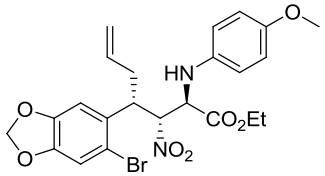


316

To a solution of crude indoline **263l** (28 mg, 78 μmol) in CH_2Cl_2 (3.5 mL) rt was added pyridine (63 μL, 0.78 mmol) followed by thiophosgene (12 μL, 0.16 mmol). The dark brown solution was stiired at rt for 1 h before being quenched with sat. aq. NH_4Cl (5 mL), extracted into CH_2Cl_2 (2 x 10 mL), washed with sat. aq. NH_4Cl (5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude thiourea **316** as a dark brown oil. Purification by flash column chromatography (30% EtOAc/Pet. ether) gave pure **316** as an off-white solid (7.0 mg, 22%); mp 192-194 °C (deg.); R_f 0.35 (30% EtOAc/Pet. ether); IR υ_{max} (neat) 3048-2836 (C-H), 1701 (C=S), 1512 (C=C), 1482, 1392, 1295, 1247 (C-O), 1176, 1035 (C-O)

cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.53 (1H, dd, *J* = 16.2, 8.9, CH_2), 2.81 (1H, dd, *J* = 16.2, 9.5, CH_2), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 5.11 (1H, q, *J* = 9.2, CH_2C*H*N), 5.43 (1H, *J* = 8.9, C*H*NPMP), 6.78 (2H, d, *J* = 8.9, Ar*H*), 6.82 (2H, d, *J* = 8.5, Ar*H*), 6.96 (1H, t, *J* = 7.3, Ar*H*), 7.02 (1H, d, *J* = 7.3, Ar*H*), 7.07 (2H, d, *J* = 8.5, Ar*H*), 7.23 (1H, t, *J* = 7.6, Ar*H*), 7.39 (2H, d, *J* = 8.9, Ar*H*), 7.57 (1H, d, *J* = 7.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.6 (*C*H_2), 55.3 (O*C*H_3), 55.5 (O*C*H_3), 60.4 (CH_2*C*HN), 63.7 (*C*HNPMP), 114.1 (Ar*C*H), 114.6 (Ar*C*H), 114.9 (Ar*C*H), 122.1 (Ar*C*H), 123.5 (Ar*C*H), 125.0 (Ar*C*H), 127.9 (Ar*C*H), 128.2 (Ar*C*H), 128.7 (Ar*C*CHN), 132.2 (Ar*C*N), 132.5 (Ar*C*CH_2), 142.4 (Ar*C*N), 155.9 (Ar*C*O), 156.2 (N_2*C*S), 159.6 (Ar*C*O); m/z (EI) 402 (25%, M^+), 281 (35%, M^+-NPMP), 236 (34%, $C_{16}H_{14}NO$); HRMS $C_{24}H_{22}N_2O_2S$ calcd. 402.1396, found 402.1402.

(2*R,3*R**,4*S**)-4-(6-Bromobenzo[1,3]dioxol-5-yl)-2-(4-methoxyphenylamino)-3-nitrohept-6-enoic acid ethyl ester (351)**



351

Diallylzinc was prepared as a 0.17 M solution in Et_2O as follows: To a stirred colourless solution of allylmagnesium bromide (1.0 M in Et_2O, 1.00 mmol) at -30 °C was added a solution of $ZnCl_2$ (0.25 M in Et_2O, 0.500 mmol) dropwise over 2 min. After 30 min at -30 °C stirring was stopped and the newly formed white ppt was allowed to settle. The colourless supernatant was removed by syringe and used immediately as a 0.17 M solution of diallylzinc (*N.B.* diallylzinc degrades readily when allowed to warm above 0 °C).

β-Nitroamine **351** was prepared as follows: To a yellow suspension of nitroalkene **352** (127 mg, 0.467 mmol) and $Cu(OTf)_2$ (8.4 mg, 23 μmol) in Et_2O (4.7 mL) at -78 °C was added freshly prepared diallylzinc (0.17 M in Et_2O, 5.49 mL, 0.933 mmol). The mixture was stirred for 30 min before being allowed to warm to rt over 90 min to form a brown precipitate. The Et_2O was removed *in vacuo* using Schlenk techniques and replaced by THF (4.7 mL). The resulting brown solution was cooled to -78 °C before a solution of imine **353** (193 mg, 0.933 mmol) in THF (2.3 mL) was added and stirred for 10 min. TFA (121 μL, 1.63 mmol) was added dropwise over 30 s and the resulting mixture stirred at -78 °C for 90 min before being allowed to warm to rt over 10 min. The reaction was quenched by the

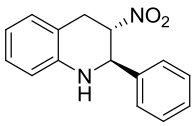
addition of sat. aq. $NaHCO_3$ (10 mL) and the product extracted into Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to leave crude *β*-nitroamine **351** as a brown oil. Purification by flash column chromatography (40% Et_2O/Pet. ether followed by 100% CH_2Cl_2) yielded pure **351** as an off-white solid (185 mg, 76%, >95:5 dr); mp 127-129 °C; R_f 0.65 (100% CH_2Cl_2); IR υ_{max} (neat) 3388 (N-H), 3072-2835 (C-H), 1740 (C=O), 1555 (N-O), 1513 (C=C), 1479, 1236 (C-O), 1036 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* = 7.2, C*H*$_3$CH$_2$O), 2.48 (1H, dt, *J* = 13.7, 8.5, C*H*$_2$CH=CH$_2$), 2.80-2.84 (1H, m, C*H*$_2$CH=CH$_2$), 3.78 (3H, s, OC*H*$_3$), 4.31 (1H, dq, *J* = 10.7, 7.1, CH$_3$C*H*$_2$O), 4.39 (1H, dq, *J* = 10.7, 7.2, CH$_3$C*H*$_2$O), 4.50 (1H, td, *J* = 9.7, 4.8, C*H*Ar), 4.62 (1H, d, *J* = 4.3, C*H*NPMP), 5.07 (1H, d, *J* = 10.0, C*H*$_2$=CH), 5.09-5.12 (1H, m, C*H*$_2$=CH), 5.13 (1H, dd, *J* = 10.3, 4.2, C*H*NO$_2$), 5.65 (1H, ddt, *J* = 17.0, 10.0, 7.1, C*H*=CH$_2$), 5.96 (1H, d, *J* = 1.0, OC*H*$_2$O), 5.98 (1H, d, *J* = 0.9, OC*H*$_2$O), 6.65-6.68 (3H, m, Ar*H*), 6.83 (2H, dm, *J* = 8.9, Ar*H*), 6.98 (1H, s, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$CH$_2$O), 36.9 (*C*H$_2$CH=CH$_2$), 43.3 (*C*HAr), 55.8 (O*C*H$_3$), 57.8 (*C*HNPMP), 62.8 (CH$_3$*C*H$_2$O), 92.3 (*C*HNO$_2$), 102.1 (O*C*H$_2$O), 107.1 (Ar*C*H), 113.2 (Ar*C*H), 115.1 (Ar*C*H), 116.2 (Ar*C*H), 116.3 (Ar*C*Br), 118.8 (*C*H=CH$_2$), 130.5 (Ar*C*CH), 133.4 (CH=*C*H$_2$), 138.7 (Ar*C*N), 147.8 (Ar*C*OCH$_2$), 147.9 (Ar*C*OCH$_2$), 153.8 (Ar*C*OCH$_3$), 169.1 (*C*O$_2$Et); m/z (ES^+) 522+524 (1:1, 20%, M^++H$_2$), 521+523 (1:1, 100%, M^++H); HRMS $C_{23}H_{26}(^{79}Br)N_2O_7$ calcd. 521.0923, found 521.0916; Anal. calcd. for $C_{23}H_{25}BrN_2O_7$: C, 52.99; H, 4.83; N, 5.37; found: C, 53.13; H, 4.79; N, 5.32%.

4.4.12 Preparation of 3-Nitrotetrahydroquinolines

General Procedure Q

To a solution of aniline (1.00 mmol) in EtOH (5.00 mL) at rt was added aldehyde (1.10 mmol) and the mixture stirred for 18 h. To this solution was added dropwise 30% aq. NH_3 (3.00 mmol) and stirred for a further 18 h. H_2O (5.0 mL) was added and the product extracted into CH_2Cl_2 (3 x 10 mL). The aqueous layer was acidified with 2 M HCl and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude 3-nitrotetrahydroquinoline which was purified by flash column chromatography.

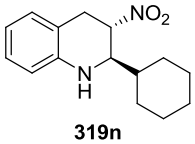
(2*R,3*S**)-3-Nitro-2-phenyl-1,2,3,4-tetrahydroquinoline (319a)**



319a

Prepared using general procedure Q. Aniline **317** (71 mg, 0.43 mmol) and benzaldehyde (50 μL, 0.47 mmol) gave crude tetrahydroquinoline **319a** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) afforded pure **319a** as a yellow solid (87 mg, 80%); mp 112-114 °C; R_f 0.46 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3403 (N-H), 3058-2908 (C-H), 1545 (N-O), 1486, 1370 cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 3.27 (1H, dd, *J* = 16.1, 4.9, C*H*$_2$), 3.59 (1H, dd, *J* = 16.1, 9.1, C*H*$_2$), 4.14 (1H, br s, N*H*), 4.89 (1H, d, *J* = 7.8, C*H*Ph), 4.95 (1H, td, *J* = 8.4, 5.0, C*H*NO_2), 6.62 (1H, d, *J* = 8.0, Ar*H*), 6.77 (1H, t, *J* = 7.4, Ar*H*), 7.08 (1H, d, *J* = 7.6, Ar*H*), 7.11 (1H, t, *J* = 8.0, Ar*H*), 7.36-7.42 (5H, m, Ar*H*); ^{1}H NMR^{syn} δ 3.21-3.35 (2H, m, C*H*$_2$), 5.09 (1H, d, *J* = 4.0, C*H*Ph), 5.14 (1H, ddd, *J* = 8.9, 5.4, 4.2, C*H*NO_2), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 31.3 (*C*H_2), 59.0 (*C*HPh), 85.3 (*C*HNO_2), 114.2 (Ar*C*H), 116.6 (Ar*C*CH_2), 118.6 (Ar*C*H), 127.3 (Ar*C*H), 128.1 (Ar*C*H), 129.2 (2 x Ar*C*H), 129.5 (Ar*C*H), 138.6 (Ar*C*CHN), 142.7 (Ar*C*N); m/z (EI) 254 (19%, M^+), 208 (12%, M^+-NO_2), 207 (35%, M^+-NO_2H), 206 (100%, M^+-NO_2H_2), 130 (41%, M^+-NO_2HPh); HRMS $C_{15}H_{14}N_2O_2$ calcd. 254.1050, found 254.1056; Anal. calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02; found: C, 70.50; H, 5.52; N, 11.10%.

(2*R,3*S**)-2-Cyclohexyl-3-nitro-1,2,3,4-tetrahydro-quinoline (319n)**

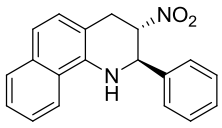


319n

Prepared using general procedure Q. Aniline **317** (94 mg, 0.57 mmol) and cyclohexane carboxaldehyde (75 μg, 0.62 mmol) gave crude tetrahydroquinoline **319n** as a brown oil. Purification by flash column chromatography (10% Et_2O/Pet. ether) afforded pure **319n** as a pale yellow oil (96 mg, 65%); R_f^{anti} 0.28 (10% Et_2O/Pet. ether); R_f^{syn} 0.22 (10% Et_2O/Pet. ether); IR υ_{max} (neat) 3419 (N-H), 3057-2852 (C-H), 1544 (N-O), 1500 (C=C), 1265 cm^{-1}; ^{1}H NMR^{anti} (600 MHz, $CDCl_3$) δ 1.06-1.30 (5H, m, Cy*H*), 1.43-1.49 (1H, m, Cy*H*), 1.70-1.92 (5H, m, Cy*H*), 3.15 (1H, dd, *J* = 16.7, 5.2, C*H*$_2$Ar), 3.51 (1H, dd, *J* = 16.7, 6.0, C*H*$_2$Ar), 3.65 (1H, td, *J* = 12.2, 2.1, C*H*NH), 3.97 (1H, br s, N*H*), 4.89 (1H, q, *J* = 5.7,

C*H*NO_2), 6.54 (1H, d, *J* = 8.3, Ar*H*), 6.71 (1H, t, *J* = 7.4, Ar*H*), 7.03-7.06 (2H, m, Ar*H*); ^{1}H NMR^{syn} (600 MHz, $CDCl_3$) δ 1.99-2.06 (2H, m, Cy*H*), 2.15 (1H, d, *J* = 12.4, Cy*H*), 3.23 (1H, dd, *J* = 17.9, 5.7, CH_2Ar), 3.36 (1H, dd, *J* = 17.7, 2.2, CH_2Ar), 3.94 (1H, br s, N*H*), 5.17 (1H, m, C*H*NO_2), 6.61 (1H, d, *J* = 7.8, Ar*H*), 6.76 (1H, t, *J* = 7.4, Ar*H*), the remaining signals could not be determined; ^{13}C NMR^{anti} (151 MHz, $CDCl_3$) δ 25.9 (Cy*C*H_2), 26.2 (Cy*C*H_2), 26.3 (Cy*C*H_2), 28.0 (Cy*C*H_2), 29.2 (*C*H_2Ar), 29.5 (Cy*C*H_2), 39.4 (Cy*C*H), 58.9 (C*H*NH), 80.8 (C*H*NO_2), 114.6 (Ar*C*H), 116.8 (Ar*C*CH_2), 118.2 (Ar*C*H), 127.7 (Ar*C*H), 129.2 (Ar*C*H), 142.1 (Ar*C*N); ^{13}C NMR^{syn} (151 MHz, $CDCl_3$) δ 38.4 (Cy*C*H), 59.2 (C*H*NH), 78.5 (C*H*NO_2), 115.2 (Ar*C*H), 117.7 (Ar*C*CH_2), 119.0 (Ar*C*H), 127.4 (Ar*C*H), 129.2 (Ar*C*H), 143.2 (Ar*C*N), the remaining signals could not be determined; m/z (EI) 260 (23%, M^+), 212 (53%, M^+-NO_2H_2), 131 (56%, M^+-(NO_2+Cy)), 130 (100%, M^+-(NO_2H+Cy)); HRMS $C_{15}H_{20}N_2O_2$ calcd. 260.1519, found 260.1521.

(2*R,3*S**)-3-Nitro-2-phenyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline (339)**



339

Prepared using general procedure Q. Aniline **330** (42 mg, 0.19 mmol) and benzaldehyde (22 μL, 0.21 mmol) gave crude tetrahydroquinoline **339** as a brown oil. Purification by flash column chromatography (10% EtOAc/Pet. ether) afforded pure **339** as a yellow solid (53 mg, 92%, >95:5 *anti*:*syn*); mp 156-158 °C; R_f 0.32 (10% EtOAc/Pet. ether); IR υ_{max} (neat) 3423 (N-H), 3060-2855 (C-H), 1577, 1547 (N-O), 1520, 1405 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.36 (1H, dd, *J* = 16.2, 4.7, CH_2), 3.74 (1H, dd, *J* = 16.2, 8.1, CH_2), 4.76 (1H, br s, N*H*), 5.03-5.08 (2H, m, C*H*Ph+C*H*NO_2), 7.19 (1H, d, *J* = 8.3, Ar*H*), 7.32 (1H, d, *J* = 8.3, Ar*H*), 7.38-7.49 (7H, m, Ar*H*), 7.71 (1H, d, *J* = 8.0, Ar*H*), 7.82 (1H, dd, *J* = 7.3, 1.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.5 (*C*H_2), 59.0 (*C*HPh), 84.7 (*C*HNO_2), 111.1 (Ar*C*CH_2), 118.8 (Ar*C*H), 119.7 (Ar*C*H), 122.6 (Ar*C*), 125.6 (Ar*C*H), 126.0 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 133.5 (Ar*C*), 137.1 (Ar*C*N), 138.6 (Ar*C*CHN); m/z (EI) 304 (18%, M^+), 256 (83%, M^+-NO_2H_2), 180 (100%, M^+-NO_2HPh); HRMS $C_{19}H_{16}N_2O_2$ calcd. 304.1206, found 304.1205.

Chapter 5: *Appendices*

5.1 Abbreviations

Å	angstrom(s)
Ac	acetyl
Anal.	analytical
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmospheres
Boc	*t*-butyloxycarbonyl
BINOL	1,1'-bi-2-naphthol
BINAP	1,1'-bis-2-naphthalene
Bn	benzyl
br	broad
Bu	butyl
Bz	benzoyl
Calcd.	calculated
CAN	ceric ammonium nitrate
cat.	Catalytic
CDI	carbonyl diimidazole
CI	chemical ionisation
cod	1,4-cyclooctadiene
conv.	conversion
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dicloro-5,6-dicyanobenzoquinone

DEAD	diethylazodicarboxylate
deg	degradation
DEPT	distortionless enhancement by polarisation transfer
DIBAL	di*iso*butylaluminium hydride
DIPEA	di*iso*propylethylamine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DOPA	3,4-dihydroxyphenylalanine
dppf	1,1'-bisdiphenylphosphinoferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv.	Equivalents
er	enantiomeric ratio
ES	electron spray
Et	ethyl
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
i	*iso*
IR	infra-red
J	coupling constant
LDA	litium di*iso*propylamide
Lit.	literature
LUMO	lowest occupied molecular orbital
M	moles per litre
m	multiplet

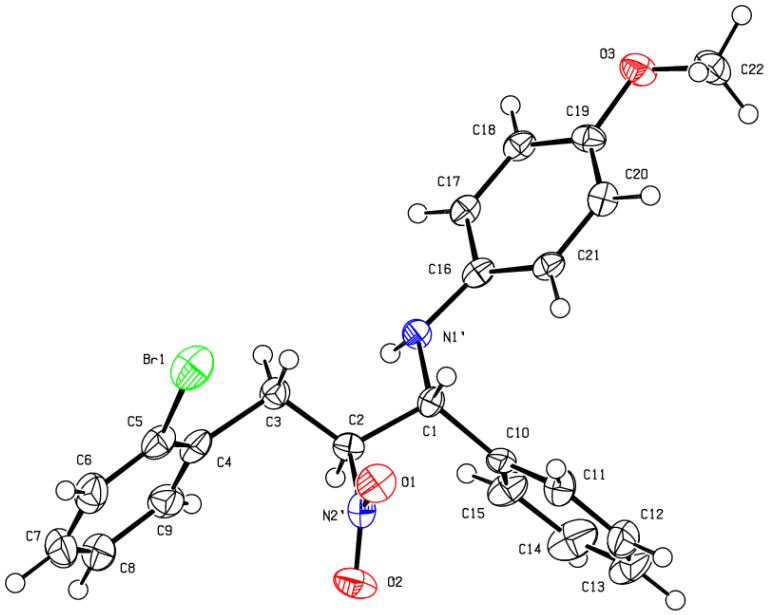
M^+	molecular ion
m	*meta*
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
n	*neo*
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl
Nu^-	nucleophile
o	*ortho*
OMB	*o*-methoxybenzyl
p	*para*
pet. ether	petroleum ether
Ph	phenyl
PMP	*p*-methoxyphenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
Py	pyridine
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
sat.	saturated

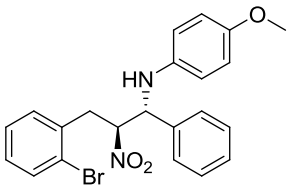
t	triplet
t	*tertiary*
T	temperature
TCA	trichloroacetic acid
TCCA	trichloro*iso*cyanuric acid
TES	triethylsilyl
TFA	trifluoroacetic acid/trifluoroacetyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMG	*N*,*N*,*N*',*N*'-tetramethylguanidine
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl
TS	transition state

5.2 X-ray Crystallography Data

All crystallographic data was collected by Prof. Alexander J. Blake and Dr. William Lewis (University of Nottingham) and Prof. Derek A. Tocher (University College London).

N-((1*R**,2*S**)-3-(2-Bromophenyl)-2-nitro-1-phenylpropyl)-4-methoxyaniline (230a)





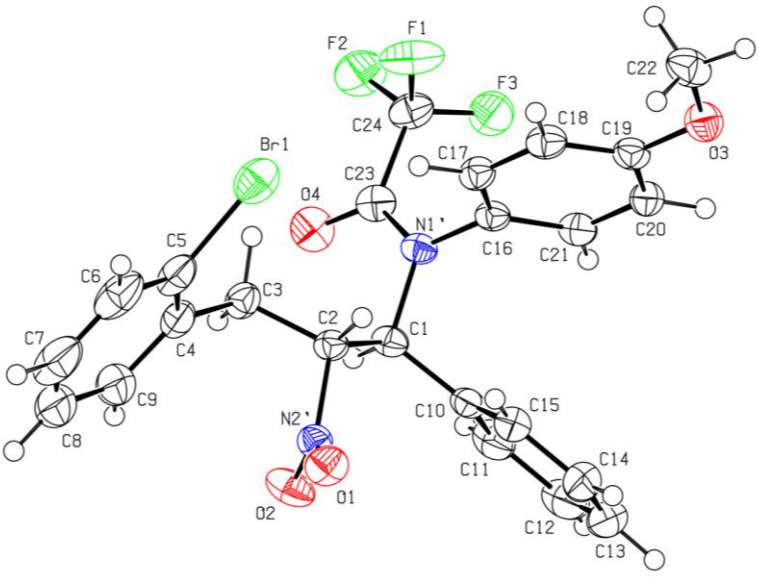
230a

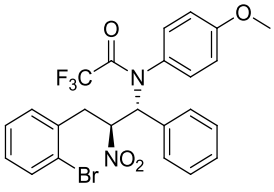
Crystal data and structure refinement for brbnnb at 150(2)K.

Empirical formula	$C_{22}H_{21}BrN_2O_3$	
Formula weight	441.32	
Crystal description	YELLOW BLOCK	
Crystal size	0.63 x 0.35 x 0.29 mm	
Crystal system	Monoclinic	
Space group	C c	
Unit cell dimensions	a = 18.3880(15) Å	α = 90°
	b = 11.6425(10) Å	β = 125.794(2)°
	c = 11.4005(19) Å	γ = 90°
Volume	1979.7(4) $Å^3$	
Reflections for cell refinement	3687	
Range in θ	2.22 to 25.77°	
Z	4	
Density (calculated)	1.481 Mg/m^3	
Absorption coefficient	2.102 mm^{-1}	
F(000)	904	
Diffractometer type	Bruker SMART APEX CCD area detector	
Wavelength	0.71073 Å	
Scan type	ω	
Reflections collected	7078	

θ range for data collection	2.22 to 25.05°
Index ranges	-21<=h<=21, -13<=k<=13, -13<=l<=13
Independent reflections	3389 [R(int) = 0.0251]
Observed reflections	3137 [I>2\s(I)]
Absorption correction	NUMERICAL (Tmin = 0.4582, Tmax = 0.7807)
Decay correction	0%
Structure solution by	direct and difmap methods
Hydrogen atom location	geom
Hydrogen atom treatment	mixed
Data / restraints / parameters	3389/10/245 (least-squares on F^2)
Final R indices [I>2σ(I)]	R1 = 0.0480, wR2 = 0.1255
Final R indices (all data)	R1 = 0.0509, wR2 = 0.1275
Goodness-of-fit on F^2	1.037
Absolute structure parameter	-0.007(12)
Final maximum delta/sigma	0.000
Weighting scheme	calc w=1/[\s^2^(Fo^2^)+(0.0847P)^2^] where P=(Fo^2^+2Fc^2^)/3
Largest diff. peak and hole	2.189 and -0.323 e.$Å^{-3}$

N-[(1*R**,2*S**)-3-(2-Bromophenyl)-2-nitro-1-phenylpropyl]-*N*-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232a)





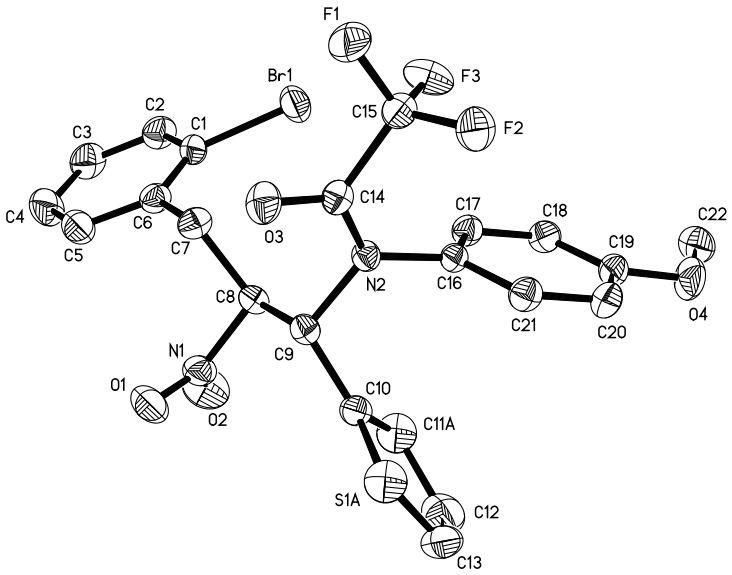
232a

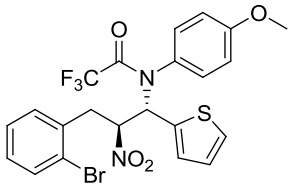
Crystal data and structure refinement for BRNOCF at 150(2)K.

Empirical formula	$C_{24}H_{20}BrF_3N_2O_4$	
Formula weight	537.33	
Crystal description	colourless block	
Crystal size	0.5 x 0.4 x 0.3 mm	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 16.6075(12) Å	α = 90°
	b = 15.5958(11) Å	β = 105.497(2)°
	c = 9.3671(7) Å	γ = 90°

Volume	2337.9(3) $Å^3$
Reflections for cell refinement	3142
Range in θ	2.5 to 23.3°
Z	4
Density (calculated)	1.527 Mg/m^3
Absorption coefficient	1.816 mm^{-1}
F(000)	1088
Diffractometer type	Bruker SMART1000 CCD area detector
Wavelength	0.71073 Å
Scan type	ω
Reflections collected	14556
θ range for data collection	2.55 to 27.47°
Index ranges	-21<=h<=21, -17<=k<=20, -7<=l<=12
Independent reflections	5234 [R(int) = 0.025]
Observed reflections	3976 [I>2sigma(I)]
Absorption correction	Semi-empirical from equivalents (Tmin = 0.649, Tmax = 0.746)
Decay correction	none
Structure solution by	direct methods
Hydrogen atom location	geometrically placed
Hydrogen atom treatment	riding model
Data / restraints / parameters	5234/0/307 (least-squares on F^2)
Final R indices [I>2σ(I)]	R1 = 0.0487, wR2 = 0.126
Final R indices (all data)	R1 = 0.0665, wR2 = 0.134
Goodness-of-fit on F^2	1.03
Final maximum delta/sigma	0.001
Weighting scheme	calc w=1/[\s^2^(Fo^2^)+(0.063P)^2^+3.031P] where P=(Fo^2^+2Fc^2^)/3
Largest diff. peak and hole	1.91 and -1.08 e.$Å^{-3}$ (both near Br1)

N-((1*S**,2*S**)-3-(2-Bromophenyl)-2-nitro-1-(thiophen-2-yl)propyl)-*N*-(4-methoxyphenyl)-2,2,2-trifluoroacetamide (232d)



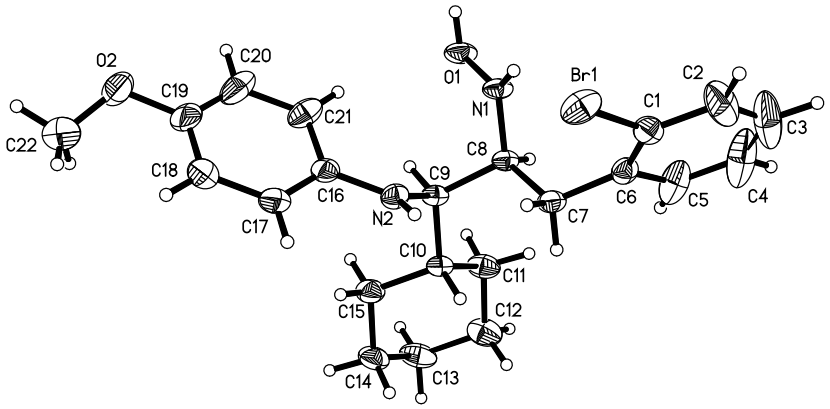


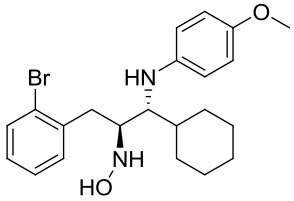
232d

Crystal data and structure refinement for str0815.

Identification code	str0815	
Chemical formula	$C_{22}H_{18}BrF_3N_2O_4S$	
Formula weight	543.35	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 14.066(2) Å	α = 90°
	b = 8.7343(13) Å	β = 93.425(2)°
	c = 18.513(3) Å	γ = 90°
Cell volume	2270.2(6) $Å^3$	
Z	4	
Calculated density	1.590 g/cm^3	
Absorption coefficient μ	1.959 mm^{-1}	
F(000)	1096	
Crystal colour and size	colourless, 0.46 × 0.46 × 0.10 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.58 to 28.29°	
Index ranges	h –18 to 18, k –11 to 11, l –23 to 23	
Completeness to θ = 26.00°	99.4 %	
Reflections collected	18148	
Independent reflections	5250 (R_{int} = 0.0378)	
Reflections with $F^2>2\sigma$	4218	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.4660 and 0.8282	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0810, 2.4371	
Data / restraints / parameters	5250 / 0 / 288	
Final R indices [$F^2>2\sigma$]	R1 = 0.0509, wR2 = 0.1363	
R indices (all data)	R1 = 0.0637, wR2 = 0.1469	
Goodness-of-fit on F^2	1.024	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	1.300 and –1.361 e $Å^{-3}$	

N-((1*R**,2*S**)-3-(2-Bromophenyl)-1-cyclohexyl-2-(hydroxyamino)propyl)-4-methoxyaniline (278)





278

Crystal data and structure refinement for str0847.

Identification code	str0847	
Chemical formula	$C_{22}H_{29}BrN_2O_2$	
Formula weight	433.38	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 9.6156(18) Å	α = 86.817(3)°
	b = 10.448(2) Å	β = 74.115(3)°
	c = 12.197(2) Å	γ = 62.824(3)°
Cell volume	1045.0(3) Å^3	
Z	2	
Calculated density	1.377 g/cm^3	
Absorption coefficient μ	1.986 mm^{-1}	
F(000)	452	
Crystal colour and size	colourless, 0.42 × 0.16 × 0.12 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
θ range for data collection	2.20 to 28.31°	
Index ranges	h –12 to 12, k –13 to 13, l –16 to 16	
Completeness to θ = 26.00°	96.7 %	
Reflections collected	8594	
Independent reflections	4589 (R_{int} = 0.0260)	
Reflections with $F^2>2\sigma$	3607	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.4893 and 0.7966	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.1049, 1.2112	
Data / restraints / parameters	4589 / 0 / 245	
Final R indices [$F^2>2\sigma$]	R1 = 0.0646, wR2 = 0.1738	
R indices (all data)	R1 = 0.0798, wR2 = 0.1899	
Goodness-of-fit on F^2	1.069	
Largest and mean shift/su	2.012 and 0.009	
Largest diff. peak and hole	1.732 and -0.994 e Å^{-3}	

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